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**ORIGINAL ARTICLE**

**Medical Economy**

# Relationship Between Heart Failure Hospitalization Costs and Left Ventricular Ejection Fraction in an Advanced Aging Society

Ryota Kaichi, MD; Kyohei Marume, MD, PhD; Michikazu Nakai, PhD; Masanobu Ishii, MD, PhD; Soshiro Ogata, PhD; Yoshitaka Iwanaga, MD, PhD; Sou Ikebe, MD; Takayuki Mori, MD; Soichi Komaki, MD; Hiroaki Kusaka, MD, PhD; Reiko Toida, MD; Kazumasa Kurogi, MD, PhD; Yoshihiro Miyamoto, MD, PhD; Nobuyasu Yamamoto, MD, PhD

***Background:*** Left ventricular ejection fraction (LVEF) is a basic clinical index that determines the heart failure (HF) treatment strategy. We aimed to evaluate the association between hospitalization costs for HF patient and LVEF in an advanced aging society in a region in Japan.

***Methods and Results:*** Consecutive HF patients admitted to Miyazaki Prefectural Nobeoka Hospital between January 2015 and March 2018 were included in the study. The 346 HF patients (mean age 78 years) were divided into 2 groups: HF with reduced ejection fraction (HFrEF; LVEF <40%; n=129) and HF with preserved ejection fraction (HFpEF; LVEF ≥40%; n=217). Median hospitalization costs (in 2017 US dollars) were higher in the HFrEF than HFpEF group, but the difference was not statistically significant ($7,128 vs. $6,580; P=0.189). However, in older adults (age ≥75 years; n=252), median hospitalization costs were significantly higher in the HFrEF than HFpEF group ($7,240 vs. $6,471; P=0.014), and LVEF was an independent factor of hospitalization costs ($\beta$=−0.0301, P=0.006). Median hospitalization costs were significantly lower in the older than younger HFpEF group ($6,471 vs. $7,250; P=0.011), but there was no significant difference in costs between the older and younger HFrEF groups ($7,240 vs. $6,760; P=0.351).

***Conclusions:*** The relationship between LVEF and hospitalization costs became more pronounced with age, and LVEF was a negative independent factor for hospitalization costs in the older population.

**Key Words:** Ejection fraction; Healthcare costs; Healthcare economics; Heart failure; Hospitalization

Heart failure (HF) is the leading cause of inpatient admissions because of the high incident ratio of first-ever hospitalization to early rehospitalization in older adults.[1,2] In 2012, over 6.5 million adults in the US had HF; in Japan, in 2005, approximately 979,000 people were diagnosed with HF.[3,4] HF patient numbers are projected to increase to 8.0 and 1.3 million in the US and Japan, respectively, by 2030.[3,4] This rapid increase is due largely to the increase in older adult patient numbers associated with the development of an aging society. In the US and Japan, 80% and 72% of HF hospitalizations are among patients aged ≥65 years[5] and ≥75 years,[1] respectively. As the number of patients with HF increases, the costs associated with HF also increase. In the US, the estimated total direct medical costs for HF were US$21 billion in 2012, an amount projected to exceed US$53 billion by 2030.[6] Thus, with the aging population in developed countries, HF has emerged as one of the most important healthcare problems, with the related costs becoming a concern regarding the economic burden on healthcare systems.[7]

HF hospitalization costs are higher for older adults because of the high HF patient numbers. However, studies have shown that costs for individual older adult patients are lower than for younger patients because older adults tend to undergo cheaper medical procedures.[1,8] Therefore,

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Miyazaki Prefectural Nobeoka Hospital, Nobeoka (R.K., K.M., M.I., S.I., T.M., S.K., H.K., R.T., K.K., N.Y.), Japan; Department of Sport Science, University of Innsbruck, Innsbruck (K.M.), Austria; and National Cerebral and Cardiovascular Center, Suita (M.N., S.O., Y.I., Y.M.), Japan

Y.M. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Kyohei Marume, MD, PhD, Department of Sport Science, University of Innsbruck, Fürstenweg 189, A-6020 Innsbruck, Austria. E-mail: Kyohhei.Marume@uibk.ac.at


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further research into HF-associated costs for older adult patients is an important part of healthcare economics and may provide evidence to support a sustainable healthcare strategy targeting HF inpatient cost reductions.

Left ventricular ejection fraction (LVEF) is a basic clinical index of HF severity, and guideline-based medical therapies are stratified according to LVEF.[9] However, there is a paucity of information regarding the association between LVEF and HF hospitalization costs, with no studies conducted in Japan.[8,10,11]

Nobeoka City (population 120,000) is relatively isolated from other urban centers, with medical care practically self-contained within the city. Miyazaki Prefectural Nobeoka Hospital is the only institution in the city with cardiovascular beds and board-certified cardiologists that can accommodate a wide range of HF patients.[12,13] Therefore, the clinical practice regarding HF in this hospital likely reflects real-world clinical practice for HF by cardiologists. Furthermore, the aging population in Nobeoka City (33% of the population is aged ≥65 years) allows us to focus on HF hospitalization costs for older adult patients. Therefore, in this study we evaluated the relationship between HF hospitalization costs and LVEF in older adult patients admitted to Miyazaki Prefectural Nobeoka Hospital.

## Methods

### Design and Study Population

Consecutive patients admitted to Miyazaki Prefectural Nobeoka Hospital for acute decompensated HF between January 2015 and March 2018 were included in this study. Nobeoka City is relatively isolated from other urban centers, with medical care is practically self-contained within the city. Miyazaki Prefectural Nobeoka Hospital serves over 230,000 people and an area of 3,185 $km^2$. During the study period, there were 4 board-certified cardiologists at the hospital. Miyazaki Prefectural Nobeoka Hospital has 410 beds, 12 and 5 of which are in the high care and intensive care units, respectively. For the general hospital beds, a 7 : 1 nursing care system is used whereby 1 nurse cares for 7 patients concurrently. Miyazaki Prefectural Nobeoka Hospital has onsite cardiac surgery backup with extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP) facilities, but it does not have facilities for heart transplantation, left ventricular assist device (LVAD) insertion, transcatheter aortic valve implantation (TAVI), or Impella (Abiomed, Danvers, MA, USA) and MitraClip (Abbott, Chicago, IL, USA) procedures.

A diagnosis of HF for patients in this study was based on the Framingham criteria; patients were assessed by 2 experienced cardiologists separately using these criteria.[14] All eligible patients represented 1 unique HF hospitalization, and all subsequent hospitalizations for the same patient during the study period were not included. In addition, patients with missing LVEF data on admission, prior heart transplants, or prior LVAD placement were excluded because these patients' costs cannot be generalized to a typical HF population. Because guideline-directed medical therapies are stratified according to an LVEF threshold of 40%,[9] patients were divided into 2 groups based on LVEF as follows: (1) HF with reduced ejection fraction (HFrEF; LVEF <40%); and (2) HF with preserved ejection fraction (HFpEF; LVEF ≥40%). Older adults were defined as those aged ≥75 years.[15–17]

This study was conducted in accordance with the Declaration of Helsinki and its amendments. The ethics committees at Miyazaki Prefectural Nobeoka Hospital (No. 20190911-1) and National Cerebral and Cardiovascular Center (No. M30-007) approved the study protocol. Because individual patients were not identified, the requirement to obtain individual consent for the study was waived. We publicized the study by posting an easy-to-understand summary of the details on a board at the hospital and on the hospital's website (https://nobeoka-kenbyo.jp/info/patient/20190215/1259/) and provided patients the opportunity to withdraw from the study.

### Data Collection

Patient demographic data, including comorbidities, clinical signs, echocardiography, and laboratory test results, were obtained at the time of admission. Echocardiography was performed using commercially available ultrasound equipment. Chamber size, wall thickness, LVEF, and tricuspid regurgitation peak gradient were evaluated using standard procedures.[18] Plasma B-type natriuretic peptide concentrations were measured using a validated, commercially available immunoassay kit (Sekisui Medical, Tokyo, Japan), and blood samples were collected in tubes containing EDTA.

Cost data were extracted from the Diagnosis Procedure Combination (DPC)/Per-Diem Payment System (PDPS), the bundled medical fees payment system for acute inpatient medical care in Japan.[19] Hospitalization costs were calculated as the sum of the bundled payment and service fee excluding the food fee, according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. The service fee was the sum of all medical service prices, such as high-cost medical procedures.[20]

### Statistical Analysis

Continuous variables are expressed as the mean ± SD, whereas variables with a skewed distribution are expressed as the median with interquartile range (IQR). Categorical variables are expressed as numbers and percentages. Data with highly skewed distributions, including HF hospitalization costs, were log transformed first before applying linear regression analysis. Categorical variables were compared using Pearson's Chi-squared test, whereas continuous variables were compared using Student's t-test or the Wilcoxon rank-sum test (for normally and non-normally distributed data, respectively). Univariate and multivariable regression analyses were used to analyze the linear relationship between log-transformed hospitalization costs (adjusted to 2017 US dollars; US$1=108 yen) and key clinical variables. Furthermore, we used an unstandardized $\beta$ to estimate the impact of each variable on log-transformed HF hospitalization costs and a standardized $\beta$ to compare the impact between each variable on log-transformed HF hospitalization costs. In order to more clearly show the effects of changes in clinical variables on HF hospitalization costs, we also calculated percentage changes in hospitalization costs using the un-standardized $\beta$ and the following equation:

$$\%\ \text{Change in hospitalization costs} = (\exp(\text{un-standardized } \beta) - 1) \times 100$$

Multivariable linear regression analysis was performed using covariates that were significantly associated with hospitalization costs on univariate analysis and those

**Table 1. Baseline Characteristics and Treatment and Outcomes of the Study Patients and in Older Adults (Age ≥75 Years) According to LVEF**

| | Total population (n=346) | | | Older adults (n=252) | | |
|---|---|---|---|---|---|---|
| | HFrEF (n=129) | HFpEF (n=217) | P value | HFrEF (n=81) | HFpEF (n=171) | P value |
| **Baseline characteristics** | | | | | | |
| Age (years) | 74±14 | 81±11 | <0.001 | 83±5 | 86±5 | 0.003 |
| Male sex | 79 (61) | 109 (50) | 0.047 | 44 (54) | 77 (45) | 0.168 |
| BMI (kg/m$^2$) | 21.8±4.3 | 21.8±4.1 | 0.919 | 20.8±3.8 | 21.1±3.8 | 0.517 |
| Ambulance use | 95 (74) | 148 (68) | 0.285 | 61 (75) | 117 (68) | 0.262 |
| Smoking history | 63 (49) | 80 (37) | 0.029 | 34 (42) | 49 (28) | 0.036 |
| De novo HF hospitalization | 85 (66) | 155 (72) | 0.280 | 54 (67) | 123 (72) | 0.393 |
| NYHA functional class | | | 0.831 | | | 0.292 |
| I | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| II | 2 (1) | 3 (1) | | 0 (0) | 2 (1) | |
| III | 37 (29) | 56 (26) | | 18 (22) | 50 (29) | |
| IV | 90 (70) | 158 (73) | | 63 (78) | 119 (70) | |
| Comorbidities | | | | | | |
| Hypertension | 89 (69) | 176 (81) | 0.010 | 56 (69) | 139 (81) | 0.031 |
| Dyslipidemia | 27 (21) | 51 (24) | 0.579 | 17 (21) | 36 (21) | 0.991 |
| Diabetes | 66 (51) | 97 (45) | 0.244 | 36 (44) | 71 (41) | 0.661 |
| AF | 47 (36) | 96 (44) | 0.154 | 31 (38) | 82 (48) | 0.149 |
| Stroke | 17 (13) | 37 (17) | 0.337 | 14 (17) | 30 (18) | 0.959 |
| CKD | 14 (11) | 36 (17) | 0.142 | 13 (16) | 29 (17) | 0.856 |
| Malignant tumor | 16 (12) | 28 (13) | 0.893 | 14 (17) | 22 (13) | 0.349 |
| Renal dialysis | 5 (4) | 7 (3) | 0.749 | 2 (2) | 3 (2) | 0.704 |
| HF etiology | | | <0.001 | | | 0.004 |
| Ischemic heart disease | 49 (38) | 63 (29) | | 32 (40) | 47 (27) | |
| Valvular disease | 19 (15) | 67 (31) | | 16 (20) | 57 (33) | |
| Cardiomyopathy | 26 (20) | 10 (5) | | 10 (12) | 5 (3) | |
| Hypertensive heart disease | 22 (17) | 45 (21) | | 14 (17) | 34 (20) | |
| Unclassified | 13 (10) | 32 (15) | | 9 (11) | 28 (16) | |
| Hemodynamic parameters | | | | | | |
| SBP (mmHg) | 144±37 | 150±35 | 0.204 | 144±32 | 148±32 | 0.367 |
| DBP (mmHg) | 93±26 | 85±24 | 0.006 | 88±22 | 82±22 | 0.061 |
| CS1 | 65 (50) | 127 (58) | 0.148 | 46 (57) | 100 (58) | 0.799 |
| Heart rate (beats/min) | 103±29 | 95±26 | 0.005 | 100±28 | 93±25 | 0.047 |
| Laboratory data | | | | | | |
| BNP (pg/mL) | 866 [516–1,934] | 458 [262–804] | <0.001 | 1,011 [601–2,080] | 479 [289–811] | <0.001 |
| Creatinine (mg/dL) | 1.52±1.25 | 1.50±1.32 | 0.864 | 1.47±0.99 | 1.35±0.97 | 0.405 |
| Albumin (g/dL) | 3.53±0.49 | 3.45±0.55 | 0.172 | 3.49±0.50 | 3.40±0.54 | 0.223 |
| Serum sodium (mEq/L) | 138.9±4.7 | 139.1±5.0 | 0.651 | 139.0±5.1 | 138.9±5.3 | 0.963 |
| Hemoglobin (g/dL) | 12.6±2.6 | 11.2±2.2 | <0.001 | 11.9±2.5 | 11.0±2.0 | 0.004 |
| CRP (mg/dL) | 0.71 [0.19–2.25] | 0.59 [0.18–2.96] | 0.168 | 0.75 [0.14–2.73] | 0.62 [0.19–3.24] | 0.369 |
| Echocardiographic variables | | | | | | |
| Septal wall thickness (mm) | 9.5±1.8 | 10.5±1.7 | <0.001 | 9.4±1.5 | 10.5±1.7 | <0.001 |
| PWT (mm) | 10.3±1.6 | 10.8±1.7 | 0.009 | 10.2±1.3 | 10.8±1.7 | 0.006 |
| Diastolic LV diameter (mm) | 55.2±7.3 | 45.4±8.0 | <0.001 | 53.4±6.2 | 44.4±7.7 | <0.001 |
| Systolic LV diameter (mm) | 47.8±7.6 | 32.8±7.5 | <0.001 | 45.7±6.2 | 31.8±7.3 | <0.001 |
| LVEF (%) | 28.9±6.7 | 53.6±9.4 | | 30.1±5.7 | 54.5±9.7 | |
| Left atrium diameter (mm) | 41.0±7.4 | 39.7±7.6 | 0.135 | 39.8±7.0 | 39.7±7.8 | 0.911 |
| TRPG (mmHg) | 34.1±14.8 | 37.7±14.2 | 0.030 | 35.1±15.8 | 39.6±14.3 | 0.029 |

(**Table 1** continued the next page.)

| Treatments and outcomes | Total population (n=346) | | | Older adults (n=252) | | |
|---|---|---|---|---|---|---|
| | HFrEF (n=129) | HFpEF (n=217) | P value | HFrEF (n=81) | HFpEF (n=171) | P value |
| Treatments/operation | | | | | | |
| Central venous injection | 3 (2) | 13 (6) | 0.117 | 2 (2) | 10 (6) | 0.239 |
| Transfusion | 6 (4) | 16 (7) | 0.316 | 6 (7) | 11 (6) | 0.773 |
| Temporary pacing | 1 (1) | 3 (1) | 0.609 | 1 (1) | 2 (1) | 0.965 |
| Pacemaker implantation | 3 (2) | 3 (1) | 0.516 | 2 (3) | 2(1) | 0.441 |
| Ventilator | 37 (29) | 63 (29) | 0.945 | 24 (30) | 41 (24) | 0.338 |
| CRRT | 2 (2) | 5 (2) | 0.630 | 1 (1) | 2 (1) | 0.965 |
| CAG | 48 (37) | 58 (27) | 0.041 | 25 (31) | 36 (21) | 0.089 |
| PCI | 11 (9) | 7 (3) | 0.032 | 8 (10) | 4 (2) | 0.009 |
| IABP | 0 (0) | 1 (0) | 0.440 | 0 (0) | 0 (0) | NA |
| ECMO | 0 (0) | 1 (0) | 0.440 | 0 (0) | 0 (0) | NA |
| Other operation | 0 (0) | 4 (2) | 0.121 | 0 (0) | 4 (2) | 0.165 |
| Myocardial perfusion scintigraphy | 5 (4) | 5 (2) | 0.399 | 2 (2) | 3 (2) | 0.704 |
| Cardiac rehabilitation | 75 (58) | 112 (51) | 0.239 | 54 (67) | 94 (55) | 0.078 |
| Discharge destination | | | 0.916 | | | 0.527 |
| Home | 93 (72) | 152 (70) | | 51 (63) | 117 (68) | |
| Hospital | 25 (19) | 42 (19) | | 22 (27) | 34 (20) | |
| Nursing facility | 4 (3) | 7 (3) | | 4 (5) | 7 (4) | |
| In-hospital death | 7 (5) | 16 (7) | | 4 (5) | 13 (8) | |
| LOS (days) | | | | | | |
| Overall LOS | 17 [12–22] | 16 [10–23] | 0.971 | 19 [13–25] | 16 [11–24] | 0.323 |
| HCU or ICU LOS (n=175) | 3 [2–4] | 3 [2–5] | 0.082 | 3 [2–5] | 3 [2–5] | 0.245 |
| Patients with any ICU or HCU stay | 64 (50) | 111 (51) | 0.782 | 44 (54) | 85 (50) | 0.494 |
| Costs ($) of bundled payment[A] | 5,751 [4,411–7,559] | 5,468 [3,804–7,372] | 0.787 | 5,900 [4,511–7,829] | 5,468 [3,781–7,409] | 0.268 |
| Costs ($) of the service fee[A] | 1,142 [770–1,597] | 997 [626–1,498] | 0.317 | 1,136 [830–1,566] | 908 [598–1,399] | 0.030 |
| Costs ($) of HF hospital stay[A] | 7,128 [5,435–9,113] | 6,580 [4,744–8,893] | 0.189 | 7,240 [5,718–9,581] | 6,471 [4,690–8,649] | 0.014 |

Data given as the mean ± SD, median [interquartile range], or n (%). [A]Costs presented in 2017 US dollars. P values presented for costs are for comparisons of log-transformed costs. AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CAG, coronary angiography; CKD, chronic kidney disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CS1, clinical scenario; DBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; HCU, high care unit; HF, heart failure; HFpEF, heart failure with preserved ejection fraction (left ventricular ejection fraction [LVEF] ≥40%); HFrEF, heart failure with reduced ejection fraction (LVEF <40%); IABP, intra-aortic balloon pumping; ICU, intensive care unit; LOS, length of hospital stay; LV, left ventricle; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PWT, posterior wall thickness; TRPG, tricuspid regurgitation pressure gradient.

related to HF hospitalization costs based on a priori clinical knowledge (age, sex, body mass index, systolic blood pressure, heart rate, prevalence of New York Heart Association [NYHA] Class IV, de novo HF hospitalization, ischemic heart disease with an etiology of HF, ambulance use, hypertension, dyslipidemia, diabetes, atrial fibrillation [AF], renal dialysis, creatinine, serum sodium, and hemoglobin concentrations, posterior wall thickness, left atrium diameter, and LVEF).[9] Stepwise selection with P=0.05 for backward elimination was used to select the best predictive model.

All statistical tests were 2-tailed and P<0.05 was considered statistically significant. All statistical analyses were performed using JMP version 9.0 (SAS Institute Japan, Tokyo, Japan) and SPSS version 20 (IBM Corp., Armonk, NY, USA).

## Results

### Patient Characteristics and Hospitalization Costs According to LVEF

Between January 2015 and March 2018, 407 patients with HF were admitted to Miyazaki Prefectural Nobeoka Hospital (mean age 78 years; 55% male, and median total hospitalization costs $6,448); of these 407 patients, 61 were excluded because of a lack of LVEF data at the time of admission, leaving 346 patients in the analysis (188 [54%] male, mean age 78 years, and mean LVEF 44.4%). The proportion of de novo HF hospitalization was 69% and the in-hospital death rate was 7%. The median total length of hospitalization was 17 days and the median total hospitalization costs were $6,780 (**Supplementary Table 1**; **Supplementary Figure 1**).

Patients were divided into 2 groups based on the LVEF: the HFrEF (n=129; 37%) and HFpEF (n=217; 63) groups. As indicated in **Table 1**, patients in the HFrEF group were significantly younger (74 vs. 81 years; P<0.001) and more likely to be male (61% vs. 50%; P=0.047) than those in the HFpEF group. There was no significant difference between the HFrEF and HFpEF groups in the proportion of de novo HF hospitalizations (66% vs. 72%, respectively; P=0.280) and NYHA Class IV patients (70% vs. 73%, respectively; P=0.831; **Table 1**). Patients in the HFrEF group had a higher prevalence of ischemic heart disease (38% vs. 29%;

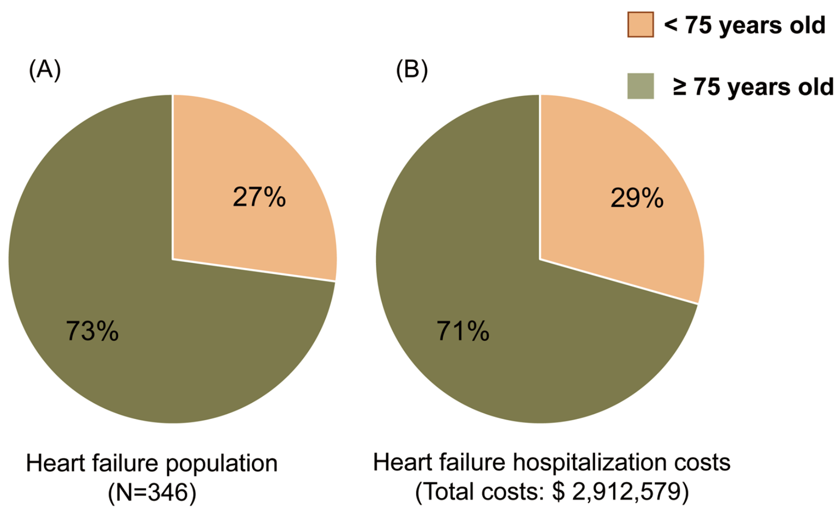


**Figure 1.** (**A**) Proportion of patients aged <75 and ≥75 years and (**B**) hospitalization costs by age.

P<0.001) and higher rates of coronary angiography (CAG; 37% vs. 27%; P=0.041) and percutaneous coronary interventions (PCI; 9% vs. 3%; P=0.032) than patients in the HFpEF group (**Table 1**). The in-hospital death rate was comparable between the 2 groups (5% vs. 7% in the HFrEF and HFpEF groups, respectively; P=0.916; **Table 1**). Although the median length of total hospitalization was longer (17 vs. 16 days; P=0.971) and total hospitalization costs were higher ($7,128 vs. $6,580; P=0.189) in the HFrEF than HFpEF group, the differences were not statistically significant (**Table 1**). LVEF tended to correlate with hospitalization costs in the univariate analysis, but this correlation was not statistically significant (un-standardized $\beta$=−0.0185, P=0.051; **Supplementary Table 2**).

## Patient Characteristics and Hospitalization Costs by LVEF in Older Adults

In this study, patients were divided into 2 groups based on age 75 years. Interaction analysis showed a significant interaction between age and LVEF with respect to hospitalization costs (P=0.038); LVEF was not associated with hospitalization costs in younger (age <75 years) adult patients (un-standardized $\beta$=0.0140, P=0.514). Older (age ≥75 years) adult patients accounted for 73% of all HF patients, and their total costs accounted for 71% of the costs for all HF patients (**Figure 1**). Older adults patients were more likely to be women (52% vs. 29%; P<0.001) and had higher LVEF (46.7% vs. 38.3%; P<0.001) than younger adult patients. Older adult patients had a higher cardiac rehabilitation rate (59% vs. 41%; P=0.004), but lower rates of other high-cost medical procedures, such as the use of ventilation (26% vs. 37%; P=0.036) and CAG (24% vs. 48%; P<0.001). Consequently, older adults had significantly lower home discharge rates (67% vs. 82%, P=0.016), slightly longer total length of hospital stay (17 vs. 15.5 days; P=0.458), and slightly lower hospitalization costs ($6,743 vs. $6,909; P=0.311) than younger patients (**Supplementary Table 1**).

**Table 1** also summarizes findings among the older adult patients according to LVEF. Older adult patients with HFrEF were more likely to be male (54% vs. 45%; P=0.168) and there was a higher prevalence of patients with NYHA Class IV (78% vs. 70%; P=0.292) than among those with HFpEF. The proportion of de novo HF hospitalization was similar in the HFrEF and HFpEF groups (67% vs. 72%, P=0.393). The prevalence of ischemic heart disease (40% vs. 27%; P=0.004) and the rate of PCI (10% vs. 2%; P=0.009) were higher among older adult patients with HFrEF than HFpEF (**Table 1**). The in-hospital death rate was comparable between the 2 groups (5% vs. 8% in the HFrEF and HFpEF groups, respectively; P=0.527). Consequently, the median length of hospital stay was slightly longer (19 vs. 16 days; P=0.323) and the median hospitalization costs were significantly higher ($7,240 vs. $6,471; P=0.014) in older adult patients with HFrEF than HFpEF. In particular, in the breakdown of the hospitalization costs, there was no significant difference in the bundled payment between the 2 groups ($5,900 vs. $5,468 in the HFrEF and HFpEF groups, respectively; P=0.268), but the service fee was significantly higher in the older HFrEF than HFpEF group ($1,136 vs. $908; P=0.030; **Table 1**).

LVEF was significantly correlated with hospitalization costs in the univariate analysis (un-standardized $\beta$=−0.0301, P=0.005), corresponding to a percentage change in hospitalization costs of −3.10% per 10% increment in LVEF. In multivariable regression analysis, LVEF was an independent factor of hospitalization costs (un-standardized $\beta$=−0.0272, P=0.025), corresponding to a percentage change in hospitalization costs of −2.68% per 10% increment in LVEF. Moreover, in the best predictive model adjusted for significant predictors selected in a stepwise linear regression analysis based on Model 1, LVEF (un-standardized $\beta$=−0.0301, P=0.006) was an independent factor of hospitalization costs in addition to systolic blood pressure, NYHA Class IV, and hemoglobin level, corresponding to a percentage change in hospitalization costs of −2.96% per 10% increment in LVEF (**Table 2**). Among these 4 variables, LVEF had the highest standardized $\beta$ (LVEF, −0.1777; systolic blood pressure, −0.1551; NYHA Class IV, 0.1720; hemoglobin level, −0.1730; **Supplementary Table 3**; **Supplementary Figure 2**).

## Age-Related Patient Characteristics and Changes in Hospitalization Costs

As a further analysis of the factors contributing to the

**Table 2. Univariate and Multivariable Linear Regression Analyses of Factors for Log-Transformed Hospitalization Costs in Older (Age ≥75 Years) Adults (n=252)**

| | Univariate analysis | | | Model 1[A] | | | Best predictive model[B] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Un-standardized β[C] | 95% CI | P value | Un-standardized β[C] | 95% CI | P value | Un-standardized β[C] | 95% CI | P value |
| Age, per 1-year increment | −0.0020 | −0.0072, 0.0040 | 0.581 | −0.0036 | −0.0097, 0.0025 | 0.244 | | | |
| Male sex | −0.0229 | −0.0849, 0.0391 | 0.468 | −0.0047 | −0.0713, 0.0618 | 0.903 | | | |
| BMI, per 1-kg/m² increment | −0.0097 | 0.0177, −0.0016 | 0.019 | −0.0050 | −0.0140, 0.0039 | 0.274 | | | |
| SBP, per 1-mmHg increment | −0.0009 | −0.0018, 0.0001 | 0.069 | −0.0009 | −0.0020, 0.0001 | 0.072 | −0.0011 | −0.0021, −0.0002 | 0.016 |
| Heart rate, per 1-beat/min increment | −0.0007 | −0.0019, 0.0005 | 0.232 | −0.0011 | −0.0024, 0.0001 | 0.071 | | | |
| NYHA Class IV | 0.0763 | 0.0077, 0.1449 | 0.029 | 0.0859 | 0.0119, 0.1600 | 0.024 | 0.0924 | 0.0252, 0.1595 | 0.007 |
| De novo HF hospitalization | 0.0102 | −0.0576, 0.0781 | 0.766 | 0.0229 | −0.0496, 0.0954 | 0.562 | | | |
| Ischemic etiology | 0.0748 | 0.0086, 0.1410 | 0.027 | 0.0302 | −0.0448, 0.1052 | 0.418 | | | |
| Ambulance use | 0.0476 | −0.0203, 0.1154 | 0.168 | 0.0445 | −0.0288, 0.1179 | 0.238 | | | |
| Comorbidities | | | | | | | | | |
| Hypertension | −0.0114 | −0.0855, 0.0627 | 0.762 | 0.0175 | 0.0594, 0.0946 | 0.634 | | | |
| Dyslipidemia | 0.0620 | −0.0138, 0.1377 | 0.108 | 0.0496 | −0.0256, 0.1249 | 0.185 | | | |
| Diabetes | 0.0456 | −0.0169, 0.1081 | 0.152 | 0.0361 | −0.0277, 0.0999 | 0.271 | | | |
| AF | −0.0200 | −0.0823, 0.0423 | 0.528 | 0.0353 | −0.0325, 0.1032 | 0.302 | | | |
| Renal dialysis | 0.1272 | −0.0947, 0.3491 | 0.260 | 0.0928 | −0.1927, 0.3784 | 0.517 | | | |
| Laboratory data | | | | | | | | | |
| Creatinine, per 1-mg/dL increment | 0.0245 | −0.0067, 0.0558 | 0.123 | −0.0002 | 0.0422, 0.0417 | 0.998 | | | |
| Serum sodium, per 1-mEq/L increment | −0.0028 | −0.0086, 0.0031 | 0.348 | −0.0019 | −0.0079, 0.0042 | 0.547 | | | |
| Hemoglobin, per 1-g/dL increment | −0.0125 | −0.0256, 0.0006 | 0.062 | −0.0162 | −0.0305, −0.0018 | 0.031 | −0.0185 | −0.0321, −0.0050 | 0.008 |
| Echocardiographic variables | | | | | | | | | |
| PWT, per 1-mm increment | −0.0261 | −0.0451, −0.0071 | 0.007 | −0.0111 | −0.0311, 0.0087 | 0.288 | | | |
| LVEF, per 10% increment | −0.0301 | −0.0520, −0.0093 | 0.005 | −0.0272 | −0.0507, −0.0036 | 0.025 | −0.0301 | −0.0514, −0.0088 | 0.006 |
| Left atrium diameter, per 1-mm increment | −0.0025 | −0.0065, 0.0016 | 0.235 | −0.0012 | −0.0057, 0.0033 | 0.605 | | | |

[A]Variables in the multivariable linear regression model were included using the simultaneous forced entry method based on significant results of the univariate analysis and factors relevant to HF hospitalization costs (i.e., age, sex, systolic blood pressure [SBP], heart rate, de novo HF hospitalization, ischemic heart disease as HF etiology, hypertension, diabetes, AF, chronic obstructive pulmonary disease, renal dialysis, creatinine levels, serum sodium levels, hemoglobin levels, and LVEF). Septal wall thickness was not used due to high collinearity. [B]Best predictive model, adjusted for significant predictors selected by stepwise linear regression using factors based on Model 1. [C]The percentage change in the hospitalization costs due to each variable can be calculated from the un-standardized β value as follows: % Change = (exp(un-standardized β) − 1) × 100. CI, confidence interval. Other abbreviations as in Table 1.

pronounced effect of LVEF on hospitalization costs in older adults, age-related patient characteristics and changes in hospitalization costs were evaluated (**Table 3**). In the HFrEF group, older adults had a significantly higher prevalence of ischemic heart disease than younger patients (40% vs. 35%; P=0.031), but the rate of CAG was similar in the 2 groups (31% vs. 48%, respectively; P=0.053). However, in the HFpEF group, older adults had a slightly lower prevalence of ischemic heart disease (27% vs. 34%; P=0.062) and a lower rate of CAG (21% vs. 48%; P<0.001)

**Table 3. Differences in Baseline Characteristics and Treatment and Outcomes for Patients in the HFrEF and HFpEF Groups According to Age**

| | HFrEF(LVEF <40%) | | | HFpEF (LVEF ≥40%) | | |
|---|---|---|---|---|---|---|
| | Age <75 years (n=48) | Age ≥75 years (n=81) | P value | Age <75 years (n=46) | Age ≥75 years (n=171) | P value |
| **Baseline characteristics** | | | | | | |
| Age (years) | 60±12 | 83±5 | <0.001 | 64±9 | 86±5 | <0.001 |
| Male sex | 35 (72) | 44 (54) | 0.036 | 32 (70) | 77 (45) | 0.003 |
| BMI (kg/m²) | 23.5±4.5 | 20.8±3.8 | <0.001 | 24.2±4.5 | 21.1±3.8 | <0.001 |
| Ambulance use | 34 (70) | 61 (75) | 0.577 | 31 (67) | 117 (68) | 0.894 |
| Smoking history | 29 (60) | 34 (42) | 0.043 | 31 (67) | 49 (28) | <0.001 |
| De novo HF hospitalization | 31 (65) | 54 (67) | 0.809 | 32 (70) | 123 (72) | 0.753 |
| NYHA functional class | | | 0.014 | | | 0.078 |
| I | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| II | 2 (4) | 0 (0) | | 1 (2) | 2 (1) | |
| III | 19 (40) | 18 (22) | | 6 (13) | 50 (29) | |
| IV | 29 (60) | 63 (78) | | 39 (88) | 119 (70) | |
| Comorbidities | | | | | | |
| Hypertension | 33 (69) | 56 (69) | 0.963 | 37 (80) | 139 (81) | 0.896 |
| Dyslipidemia | 10 (21) | 17 (21) | 0.983 | 15 (32) | 36 (21) | 0.101 |
| Diabetes | 30 (62) | 36 (44) | 0.047 | 26 (57) | 71 (41) | 0.069 |
| AF | 16 (33) | 31 (38) | 0.573 | 14 (30) | 82 (48) | 0.034 |
| Stroke | 3 (6) | 14 (17) | 0.073 | 7 (15) | 30 (18) | 0.709 |
| CKD | 1 (2) | 13 (16) | 0.014 | 7 (15) | 29 (17) | 0.778 |
| Malignant tumor | 2 (4) | 14 (17) | 0.029 | 6 (13) | 22 (13) | 0.974 |
| Renal dialysis | 3 (6) | 2 (2) | 0.282 | 4 (9) | 3 (2) | 0.018 |
| HF etiology | | | 0.031 | | | 0.062 |
| Ischemic heart disease | 17 (35) | 32 (40) | | 16 (34) | 47 (27) | |
| Valvular disease | 3 (6) | 16 (20) | | 10 (21) | 57 (33) | |
| Cardiomyopathy | 16 (33) | 10 (12) | | 5 (11) | 5 (3) | |
| Hypertensive heart disease | 8 (16) | 14 (17) | | 11 (23) | 34 (20) | |
| Unclassified | 4 (8) | 9 (11) | | 4 (9) | 28 (16) | |
| Hemodynamic parameters | | | | | | |
| SBP (mmHg) | 145±44 | 144±32 | 0.899 | 155±44 | 148±32 | 0.253 |
| DBP (mmHg) | 100±30 | 88±22 | 0.008 | 95±27 | 82±22 | <0.001 |
| CS1 | 19 (40) | 46 (57) | 0.059 | 27 (59) | 100 (58) | 0.979 |
| Heart rate (beats/min) | 110±28 | 100±28 | 0.034 | 105±26 | 93±25 | 0.003 |
| Laboratory data | | | | | | |
| BNP (pg/mL) | 789 [439–1,321] | 1,011 [601–2,080] | 0.147 | 434 [221–591] | 479 [289–811] | 0.367 |
| Creatinine (mg/dL) | 1.27±0.76 | 1.35±0.67 | 0.488 | 1.75±1.56 | 1.27±0.70 | 0.002 |
| Albumin (g/dL) | 3.61±0.48 | 3.49±0.50 | 0.198 | 3.63±0.55 | 3.40±0.54 | 0.014 |
| Serum sodium (mEq/L) | 138.7±4.1 | 139.0±5.1 | 0.772 | 139.8±3.7 | 138.9±5.3 | 0.289 |
| Hemoglobin (g/dL) | 13.8±2.1 | 11.9±2.5 | <0.001 | 12.1±2.6 | 11.0±2.0 | 0.002 |
| CRP (mg/dL) | 0.63 [0.22–2.11] | 0.75 [0.14–2.73] | 0.273 | 0.47 [0.13–2.35] | 0.62 [0.19–3.24] | 0.411 |
| Echocardiographic variables | | | | | | |
| Septal wall thickness (mm) | 9.8±2.3 | 9.4±1.5 | 0.153 | 10.7±1.7 | 10.5±1.7 | 0.654 |
| PWT (mm) | 10.6±2.1 | 10.2±1.3 | 0.185 | 11.0±1.9 | 10.8±1.7 | 0.438 |
| Diastolic LV diameter (mm) | 58.3±8.2 | 53.4±6.2 | <0.001 | 49.3±8.1 | 44.4±7.7 | <0.001 |
| Systolic LV diameter (mm) | 51.3±8.4 | 45.7±6.2 | <0.001 | 36.6±7.2 | 31.8±7.3 | <0.001 |
| LVEF (%) | 26.9±7.9 | 30.1±5.7 | <0.001 | 50.1±7.3 | 54.5±9.7 | 0.004 |
| Left atrium diameter (mm) | 42.9±7.8 | 39.8±7.0 | 0.021 | 39.8±6.9 | 39.7±7.8 | 0.944 |
| TRPG (mmHg) | 32.4±13.1 | 35.1±15.8 | 0.346 | 29.7±11.0 | 39.6±14.3 | <0.001 |

(**Table 3** continued the next page.)

| | HFrEF(LVEF <40%) | | | HFpEF (LVEF ≥40%) | | |
|---|---|---|---|---|---|---|
| | Age <75 years (n=48) | Age ≥75 years (n=81) | P value | Age <75 years (n=46) | Age ≥75 years (n=171) | P value |
| **Treatments and outcomes** | | | | | | |
| Expensive treatments and examinations | | | | | | |
| Central venous injection | 1 (2) | 2 (2) | 0.888 | 3 (7) | 10 (6) | 0.864 |
| Transfusion | 0 (0) | 6 (7) | 0.054 | 5 (11) | 11 (6) | 0.307 |
| Temporary pacing | 0 (0) | 1 (1) | 0.439 | 1 (2) | 2 (1) | 0.605 |
| Pacemaker implantation | 1 (2) | 2 (3) | 0.888 | 1 (2) | 2(1) | 0.605 |
| Ventilator | 13 (27) | 24 (30) | 0.757 | 22 (48) | 41 (24) | 0.002 |
| CRRT | 1 (2) | 1 (1) | 0.706 | 3 (7) | 2 (1) | 0.032 |
| CAG | 23 (48) | 25 (31) | 0.053 | 22 (48) | 36 (21) | <0.001 |
| PCI | 3 (6) | 8 (10) | 0.476 | 3 (7) | 4 (2) | 0.154 |
| IABP | 0 (0) | 0 (0) | NA | 1 (2) | 0 (0) | 0.053 |
| ECMO | 0 (0) | 0 (0) | NA | 1 (2) | 0 (0) | 0.053 |
| Other operation | 0 (0) | 0 (0) | NA | 0 (0) | 4 (2) | 0.295 |
| Myocardial perfusion scintigraphy | 3 (6) | 2 (2) | 0.282 | 2 (4) | 3 (2) | 0.298 |
| Cardiac rehabilitation | 21 (44) | 54 (67) | 0.011 | 18 (40) | 94 (55) | 0.056 |
| Discharge destination (%) | | | 0.008 | | | 0.501 |
| Home | 42 (87) | 51 (63) | | 35 (76) | 117 (68) | |
| Hospital | 3 (6) | 22 (27) | | 8 (17) | 34 (20) | |
| Nursing facility | 0 (0) | 4 (5) | | 0 (0) | 7 (4) | |
| In-hospital death | 3 (6) | 4 (5) | | 3 (6) | 13 (8) | |
| LOS (days) | | | | | | |
| Overall LOS | 16 [11–20] | 19 [13–25] | 0.042 | 15 [9–21] | 16 [11–24] | 0.628 |
| HCU or ICU LOS | 3 [2–3] | 3 [2–5] | 0.075 | 2 [2–4.25] | 3 [2–5] | 0.271 |
| Patients with any ICU or HCU stay | 28 (58) | 44 (54) | 0.165 | 20 (43) | 85 (50) | 0.412 |
| Costs ($) of the bundled payment[A] | 5,495 [3,891–7,115] | 5,900 [4,511–7,829] | 0.124 | 5,438 [3,848–7,388] | 5,468 [3,781–7,409] | 0.483 |
| Costs ($) of the service fee[A] | 1,184 [476–1,676] | 1,136 [830–1,566] | 0.579 | 1,289 [850–1,759] | 908 [598–1,399] | 0.006 |
| Costs ($) of HF hospital stay[A] | 6,760 [4,690–8,478] | 7,240 [5,718–9,581] | 0.351 | 7,250 [4,979–10,568] | 6,471 [4,690–8,649] | 0.011 |

Data given as the mean ± SD, median [interquartile range], or n (%). [A]Costs presented in 2017 US dollars. P values presented for costs are for comparisons of log-transformed costs. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction. Other abbreviations as in Table 1.

than younger patients. The proportion of patients with NYHA Class IV was significantly higher in the older than younger HFrEF group (78% vs. 60%; P=0.014), but similar in the older and younger HFpEF groups (70% vs. 88%, respectively; P=0.078). These changes in HF severity may have contributed to the finding of a similar rate of ventilation use in the older and younger HFrEF groups (30% vs. 27%, respectively; P=0.757) but a lower rate in the older than younger HFpEF group (24% vs. 48%; P=0.002). Moreover, compared with younger HFrEF patients, the higher prevalence of chronic kidney disease (CKD; 16% vs. 2%; P=0.014) and malignancy (17% vs. 4%; P=0.029) in the older HFrEF group may be related to the lower hemoglobin levels in the older than younger patients (11.9 vs. 13.8 mg/dL; P<0.001), which resulted in slightly higher transfusion rates in the older patients (7% vs. 0%; P=0.054). These factors may have contributed to the longer length of hospital stay (19 vs. 16 days; P=0.042) and lower home discharge rates (63% vs. 87%; P=0.008) in the older than younger HFrEF group, and the similarities between the older and younger HFpEF groups in length of hospital stay (16 vs. 15 days, respectively; P=0.628) and home discharge rates (68% vs. 76%, respectively; P=0.501). Consequently, total hospitalization costs were similar for older and younger HFrEF patients ($7,240 vs. $6,760, respectively; P=0.351), but significantly lower for older than younger HFpEF patients ($6,471 vs. $7,250; P=0.011). Furthermore, the bundled payment was similar between the older and younger HFpEF groups ($5,468 vs. $5,438, respectively; P=0.483), but the service fee was significantly lower for the older than younger HFpEF group ($908 vs. $1,289; P=0.006; **Table 3**).

## Discussion

The main findings of this study were that: (1) LVEF was a negative independent factor of hospitalization costs in older adults with HF; and (2) the relationship between LVEF and hospitalization costs became more pronounced with age (i.e., with increasing age, the service fee decreased in the HFpEF group, but remained the same in the HFrEF group). To the best of our knowledge, this is the first study to investigate the relationship between HF hospitalization costs and LVEF in Japan. Our results provide evidence for the development of future novel healthcare strategies, especially for cost reductions for older adult inpatients with HF.

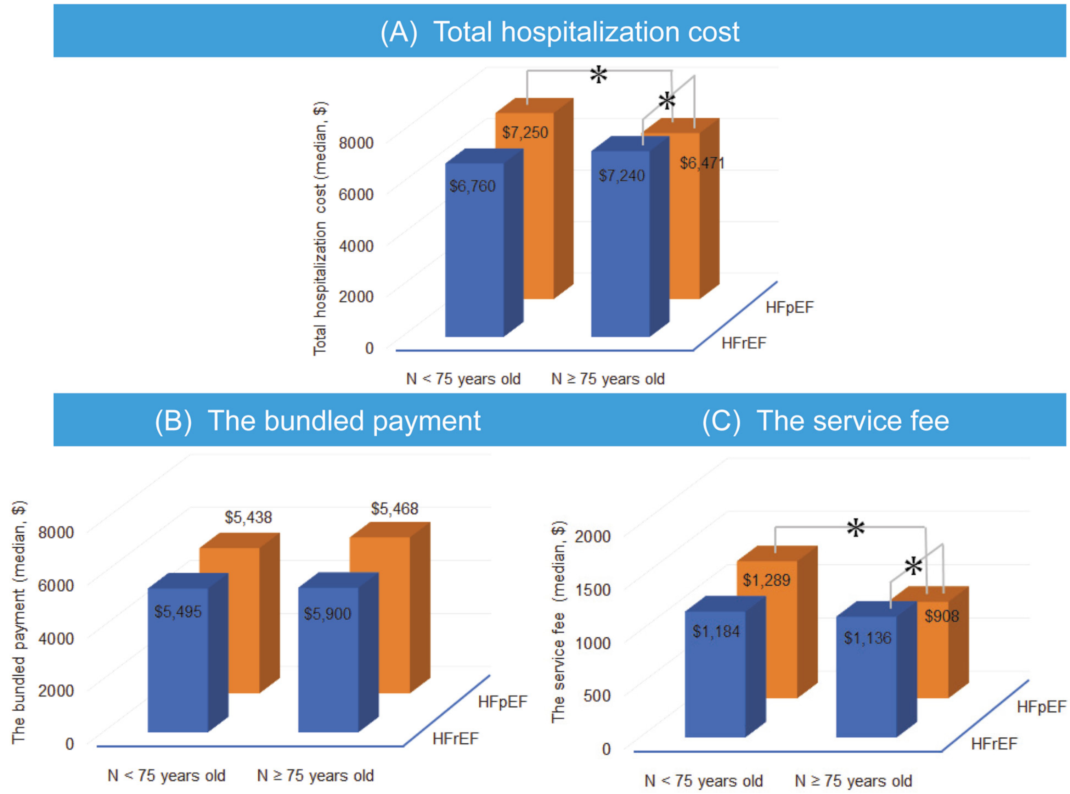


**Figure 2.** Median hospitalization costs by age and left ventricular ejection fraction (LVEF): (**A**) total hospitalization costs, (**B**) bundled payment by age, and (**C**) service fee. *P<0.05. HFpEF, heart failure with preserved ejection fraction (LVEF ≥40%); HFrEF, heart failure with reduced ejection fraction (LVEF <40%).

### Association Between LVEF and HF Hospitalization Costs

Few studies have investigated the association between LVEF and HF hospitalization costs. A population-based study in Olmsted County (MN, USA) investigated the lifetime healthcare costs for 1,043 individuals with HF.[8] HF patients were enrolled in that study after their initial diagnosis and were followed up from 1987 to 2006. After adjusting for age, year of diagnosis, and comorbidities, HFpEF (≥50%) was associated with 20.7% higher lifetime inpatient costs (P=0.041).[8] Even though the patients in that study were of a similar age as those in the present study (mean age 76 vs. 78 years, respectively), we found a trend for higher hospitalization costs for HFrEF patients in the present study. The reasons for this discrepancy may be that HFpEF had a higher all-cause and non-cardiovascular readmission rate than HFrEF,[21,22] or because high-cost treatments for ischemic heart disease were underdeveloped at the time of the previous trial. Olchanski et al investigated the demographic and clinical predictors of higher hospitalization costs in an academic hospital setting.[10] In that single-center observational study of 564 patients with decompensated HF admitted between 2010 and 2013, there was a trend towards higher median HF hospitalization costs in patients with HFrEF than HFpEF ($10,286 vs. $8,858; P=0.07).[10] Furthermore, LVEF was not a demographic predictor of cost ($\beta$=0.0026, P=0.28) in their multivariable regression analysis.[10] A European study that included 197 HF patients also found that mean total costs per hospitalization were higher among patients with LVEF <30% than among those with LVEF ≥30% (€3,672 vs. €2,618; P=0.001), but LVEF was not a demographic predictor of costs.[11] Our finding from a Japanese hospital of a trend for higher HF hospitalization costs for patients with HFrEF compared with HFpEF is consistent with previous finding reported in other countries. In addition to presenting detailed post-hospitalization patient characteristics, our data add to the findings of these previous studies by demonstrating that the relationship between LVEF and hospitalization costs became more pronounced with age.

### Effect of Aging on the Association Between LVEF and HF Hospitalization Costs

A US study showed a negative predictive change in inpatient costs for those aged 75–84 and ≥85 years compared with those aged ≤55 years (−63.8% and −113.9%, respectively; P=0.001 for both).[8] A study from the Japanese Registry of All Cardiac and Vascular Diseases also concluded that younger patients are treated with "aggressive" strategies and that older adult patients are treated with "conservative" strategies, because high-medical-cost treatments, such as PCI, IABP, and ECMO, were more common in the younger population.[1] This is consistent with the results of the present study, which show a trend for lower service fees in the older compared with younger HFpEF group. However, a different trend was observed in the HFrEF group, in which the service fee remained the same regardless of age (**Figure 2**).

Based on our data, we propose 3 reasons for the differences in changes in service fees with age between the HFrEF and HFpEF groups. First, the CAG rate was lower in older adult patients in the HFpEF group, whereas the CAG rate was similar in younger and older patients in the HFrEF group. We found a significant increase in the ischemic etiology of HF related to age in the HFrEF group, which is consistent with the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-I and -II studies, in which the percentage of patients with an ischemic etiology of HF increased with age (26.4% and 47.1% in CHART-I and CHART-II, respectively).[23,24] The CHART-I and CHART-II studies also reported that treatment advances, including PCI, have reduced cardiovascular morbidity and mortality, resulting in an increased ischemic heart disease prevalence in the senior older adult population.[23,24] Moreover, compared with younger patients, older adult patients with ischemic heart disease have more severe and diffuse coronary atherosclerosis that requires catheter examinations and treatment.[25] Second, transfusion rates were similar between younger and older patients in the HFpEF group, whereas they tended to be higher in older than younger patients in the HFrEF group. We also found a significant age-related increase in the prevalence of CKD and anemia in the HFrEF group. These factors are associated with worse HF symptoms.[26] In addition, long-term antiplatelet therapy for ischemic heart disease is a high-risk factor for gastrointestinal bleeding and anemia.[27] Third, the aforementioned age-related changes in the HFrEF group may have worsened the severity of HF (i.e., a greater prevalence of NYHA Class IV), which affected the use of ventilation.

Current clinical practice increasingly requires that cardiologists make decisions about the indications for examinations and treatments with an expensive service fee, including CAG, ventilation use, and transfusions, for older HFrEF patients in aging societies, among which Japan is at the forefront. Due to the lack of guiding evidence for the treatment of this population, further studies are required to determine the optimal medical strategy. However, careful consideration of the content and timing of medical examinations, as well as treatments, for the sickest older HFrEF patients is necessary to achieve sustainable HF health care.

### Study Limitations

This study has several limitations. First, the study population was relatively small. For generalization to HF cases observed in most hospitals, it was important to include patients admitted only to Miyazaki Prefectural Nobeoka Hospital, which, during the study period, was the only regional, high-quality, acute care hospital with facilities to offer specialized tests and provide standard HF care with 4 board-certified cardiologists. However, patients with missing LVEF data at the time of admission were excluded from the study. Compared with the enrolled study population, the excluded patients had a significantly shorter total length of hospital stay (12 vs. 17 days; P=0.002) and lower hospitalization costs ($4,550 vs. $6,780; P<0.001), a lower proportion of had NYHA Class IV (38% vs. 72%; P<0.001). Therefore, when considering the findings, it should be kept in mind that a certain number of patients with low HF severity were excluded from the analysis.

Second, with the DPC/PDPS, it was difficult to clearly calculate the actual expenditure components in each case because this decision process was not fully disclosed. Third, this study did not include LVAD, TAVI, and Impella and MitraClip procedures. However, the exclusion of these highest-acuity patients increased the generalizability of our analysis to the HF cases seen in most hospitals. Finally, the length of stay in Japanese hospitals is longer than in the US and Europe (4–11 days),[28,29] with the median length of hospital stay in the present study being 17 days. Possible reasons for this difference are that: (1) Japan has a greater number of beds per 1,000 people than other countries;[30,31] and (2) the DPC-based payment system is a "per-day payment" system, which is different from the "per-case payment" diagnostic-related group/prospective payment system. Shortening the duration of the hospital stays does not necessarily increase each hospital's profits, particularly in cardiovascular medicine.[20]

Because of these limitations, an external validation study should be conducted to confirm our results.

## Conclusions

The relationship between LVEF and hospitalization costs became more pronounced with age, and LVEF was a negative independent factor of hospitalization costs in a population aged ≥75 years. This is because as treatment for HF changed with age, the individual hospitalization costs decreased in HFpEF but not HFrEF patients.

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### Disclosures

Y.M. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to declare.

### IRB Information

This study was approved by Miyazaki Prefectural Nobeoka Hospital (Reference no. 20190911-1) and the National Cerebral and Cardiovascular Center (Reference no. M30-007).

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## Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-21-0134