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ORIGINAL ARTICLE
Heart Failure

Incidence and Clinical Significance of 30-Day and 90-Day Rehospitalization for Heart Failure Among Patients With Acute Decompensated Heart Failure in Japan
— From the NARA-HF Study —

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Background: Countermeasure development for early rehospitalization for heart failure (re-HHF) is an urgent and important issue in Western countries and Japan.

Methods and Results: Of 1,074 consecutive NARA-HF study participants with acute decompensated HF admitted to hospital as an emergency between January 2007 and December 2016, we excluded 291 without follow-up data, who died in hospital, or who had previous HF-related hospitalizations, leaving 783 in the analysis. During the median follow-up period of 895 days, 241 patients were re-admitted for HF. The incidence of re-HHF was the highest within the first 30 days of discharge (3.3% [26 patients]) and remained high until 90 days, after which it decreased sharply. Within 90 days of discharge, 63 (8.0%) patients were re-admitted. Kaplan-Meier analysis revealed that patients with 90-day re-HHF had worse prognoses than those without 90-day re-HHF in terms of all-cause death (hazard ratio [HR] 2.321, 95% confidence interval [CI] 1.654–3.174; P<0.001) and cardiovascular death (HR 3.396, 95% CI 2.153–5.145; P<0.001). Multivariate analysis indicated that only male sex was an independent predictor of 90-day re-HHF.

Conclusions: The incidence of early re-HHF was lower in Japan than in Western countries. Its predictors are not related to the clinical factors of HF, indicating that a new comprehensive approach might be needed to prevent early re-HHF.

Key Words: Acute decompensated heart failure; Early rehospitalization; Predictors

Heart failure (HF) is one of the most common causes of hospitalization with high mortality, and its worldwide prevalence is increasing.[1,2] Despite remarkable progress in outcomes for HF,[3,4] the rate of early rehospitalization for HF (re-HHF) remains high.[5] The rate of 30-day HF rehospitalization in the claims databases of the USA and in worldwide randomized clinical trials is 20–25%[6–10] and 5–10%,[11,12] respectively. Previous studies indicated that patients who were re-admitted within 30 days after discharge had a poor prognosis.[11,13,14] Many factors, such as HF severity, quality of medical therapy, insurance system, availability of multidisciplinary support, and the length of hospital stay, may influence early rehospitalization, but the specific risk factors are not well known. Although the length of hospital stay has been reported to be related to rates of early rehospitalization,[12,15] previous studies have not included Japanese patients. Because the medical care system in Japan, which is a universal insurance system, is unique and quite different from that in the USA and Europe, the mean length of hospital stay in Japan is around 17 days,[16] which is much longer than in other countries.

This study aimed to assess the incidence, timing, and clinical significance of HF rehospitalization after discharge in Japan to provide suggestions for improving medical care and prevent early HF rehospitalization.

Methods

Study Population

The NARA-HF 3 study, which has been described previously,[17,18] recruited 1,074 consecutive patients with acute decompensated HF (ADHF) who were emergently admitted to hospital between January 2007 and December 2016.

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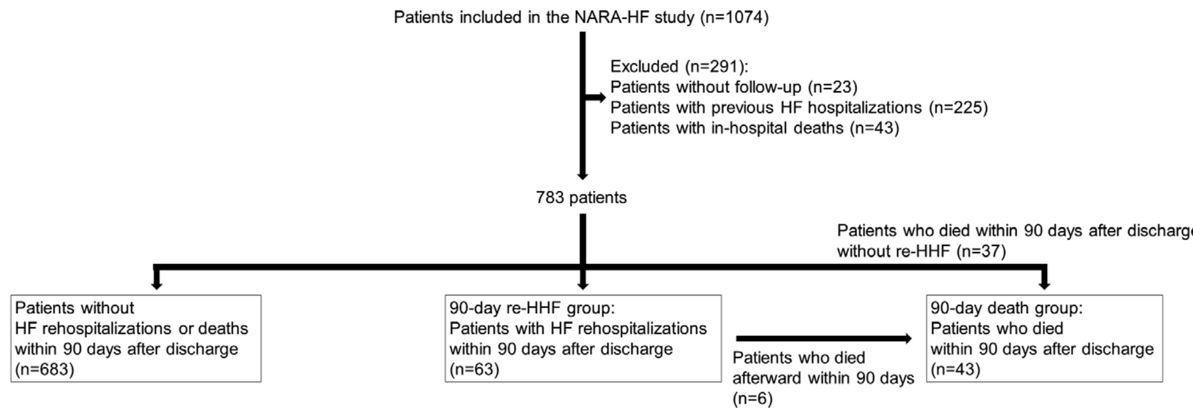

Figure 1. Flowchart of study population. HF, heart failure; re-HHF, rehospitalization for HF.

The diagnosis of HF was based on the criteria of the Framingham study,[19] and hospitalization for HF was defined as admission for worsening signs or symptoms of HF resulting in the adjustment of HF therapies. Patients with acute myocardial infarction, acute myocarditis, and acute HF with acute pulmonary embolism were excluded from the NARA-HF study. In the current analysis, we excluded patients who were lost to follow-up, had previous HF hospitalization, or died during the index hospitalization. Baseline data, including age, sex, body mass index (BMI), length of hospitalization, HF etiology, medical history, vital signs, laboratory and echocardiographic data, and medications at discharge, were collected. For analysis the patients were categorized into those with and without 90-day re-HHF.

This study was approved by the Ethics Committee of Nara Medical University (approval no. 624) and complied with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Written informed consent was given by all patients.

Outcomes

The outcomes of interest for this study were all-cause and cardiovascular death in patients with or without 90-day re-HHF. Cardiovascular death was defined as death from HF, myocardial infarction, sudden death, stroke, or vascular disease. We focused on the 90-day interval between discharge and readmission and examined the predictors of 90-day re-HHF and all-cause death.

The vital status and cause of death were determined from patients' medical records. If this information was unavailable, the patient or family was contacted to collect the data.

Statistical Analysis

Normally and non-normally distributed data are expressed as mean±SD and as median and interquartile range, respectively. Categorical variables were summarized as percentages and compared using the chi-squared test, while continuous variables were compared using Student's t-test for normally distributed data or the Wilcoxon rank-sum test for non-normally distributed data. First, the prognostic differences in death between groups were assessed using the Kaplan-Meier method and compared via log-rank test. The association between 90-day re-HHF and all-cause or cardiovascular death was assessed via Cox proportional hazard models in univariate and multivariate analyses, and the results are reported as hazard ratio (HR) with 95% confidence interval (CI). An unadjusted model and 7 adjusted models with covariates that were already known as prognostic factors or risk factors of HF were utilized: model 1, adjusted for age and sex; model 2, adjusted for all factors in model 1 plus hemoglobin level, estimated glomerular filtration rate (eGFR), and B-type natriuretic peptide (BNP) level at discharge; model 3, adjusted for all factors in model 2 plus systolic blood pressure and heart rate at discharge; model 4, adjusted for all factors in model 3 plus left ventricular ejection fraction (LVEF); model 5, adjusted for all factors in model 4 plus medical history of diabetes mellitus and atrial fibrillation; model 6, adjusted for all factors in model 5 plus causes of HF; and model 7, adjusted for all factors in model 6 plus medications at discharge. Next, we investigated the independent predictors of 90-day re-HHF and 90-day all-cause death using univariate and multivariate proportional hazard models. In the multivariate analysis of predictors of 90-day re-HHF, we used the variables that were statistically significant in the univariate analysis and age, because it is known to be a strong prognostic factor of HF. In the multivariate analysis to identify predictors of 90-day all-cause death, we used the covariates that were statistically significant in the univariate analysis. The results are also reported as HR with 95% CI. JMP software for Windows version 14 (SAS Institute, Cary, NC, USA) was used for all statistical analyses, and $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Study Population

Of the 1,074 patients in the NARA-HF 3 study, we excluded 23 who were lost to follow-up, 225 with previous HF hospitalization, and 43 who died during the index hospitalization. Consequently, 783 patients who were hospitalized for HF for the first time and were discharged alive were included in the present study (**Figure 1**). The baseline characteristics of the study population are shown in **Table 1**. The mean age was 73.3±12.3 (mean±SD) years, and males accounted for 55.2% of the population. The

Table 1. Baseline Characteristics of the Study Population

	All patients (n=783)	Without 90-day re-HHF or death (n=683)	With 90-day re-HHF (n=63)	P value
Demographics				
Age (years)	73.3±12.3	72.8±12.6	75.0±9.2	0.174
Male (%)	55.2	53.7	66.7	0.046
BMI (kg/m^2)	23.4±4.2	23.6±4.3	23.2±3.5	0.458
NYHA class 3 or 4 on admission (%)	89.8	89.2	93.7	0.236
NYHA class 3 or 4 at discharge (%)	4.5	4.8	3.2	0.538
Length of hospitalization (days)	19 [13–29]	19 [13–29]	21 [12–28]	0.964
Discharged home (%)	88.3	89.5	93.7	0.264
Cause of HF, %				
Ischemic heart disease	37.0	36.5	44.4	0.214
Dilated cardiomyopathy	14.4	15.2	9.5	0.198
Hypertensive heart disease	7.7	7.9	7.9	0.993
Valvular heart disease	15.8	15.7	15.9	0.966
Medical history, %				
Diabetes mellitus	46.2	45.1	55.6	0.112
AF	32.1	31.2	36.5	0.390
Vital signs on admission				
Heart rate (beats/min)	97.7±27.7	97.9±27.7	95.4±27.6	0.491
SBP (mmHg)	148.8±35.9	149.6±35.9	147.9±32.3	0.715
Vital signs at discharge				
Heart rate (beats/min)	71.7±11.6	71.5±11.1	70.3±12.0	0.446
SBP (mmHg)	113.4±18.3	113.4±17.9	116.7±20.7	0.166
Echocardiographic parameters at discharge				
LVEF (%)	45.9±16.6	45.7±16.5	47.6±16.3	0.388
LVEF ≥50% (%)	39.5	39.2	38.1	0.822
Laboratory data on admission				
BNP (pg/mL)	892 [457–1,591]	886 [451–1,570]	817 [519–1,383]	0.937
Hemoglobin (g/dL)	11.5±2.4	11.6±2.4	11.2±2.4	0.191
eGFR (mL/min/1.73 m^2)	46.1±27.3	47.1±27.6	39.0±24.0	0.026
BUN (mg/dL)	30.6±21.7	29.6±21.0	33.5±19.6	0.153
CRP (mg/dL)	0.6 [0.2–2.2]	0.5 [0.2–2.0]	0.9 [0.2–3.4]	0.042
Sodium (mEq/L)	138.6±4.2	138.7±4.1	137.9±4.5	0.159
Laboratory data at discharge				
BNP (pg/mL)	251 [132–486]	234 [129–464]	310 [130–660]	0.327
Hemoglobin (g/dL)	11.5±2.1	11.5±2.1	11.1±1.9	0.148
eGFR (mL/min/1.73 m^2)	42.8±25.0	43.3±25.4	35.7±20.0	0.022
BUN (mg/dL)	32.1±18.4	31.1±17.7	38.0±20.3	0.004
CRP (mg/dL)	0.4 [0.1–1.0]	0.3 [0.1–1.0]	0.5 [0.1–1.3]	0.734
Sodium (mEq/L)	137.9±3.8	138.0±3.7	137.0±4.8	0.053
Medications at discharge				
β-blocker (%)	59.4	58.6	60.3	0.787
ACEI/ARB (%)	87.7	88.6	86.9	0.695
MRA (%)	34.2	34.9	28.6	0.309
Diuretic (%)	78.7	78.4	82.5	0.434
Loop diuretic (%)	77.3	77.0	81.0	0.459

Data are presented as the mean ± SD for continuous normally distributed variables, the median (25–75th interquartile range) for continuous non-normally distributed variables, or n (%). P-values are generated from the comparison of the patients without 90-day re-HHF or death vs. the patients with 90-day re-HHF. ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; re-HHF, rehospitalization for heart failure; SBP, systolic blood pressure.

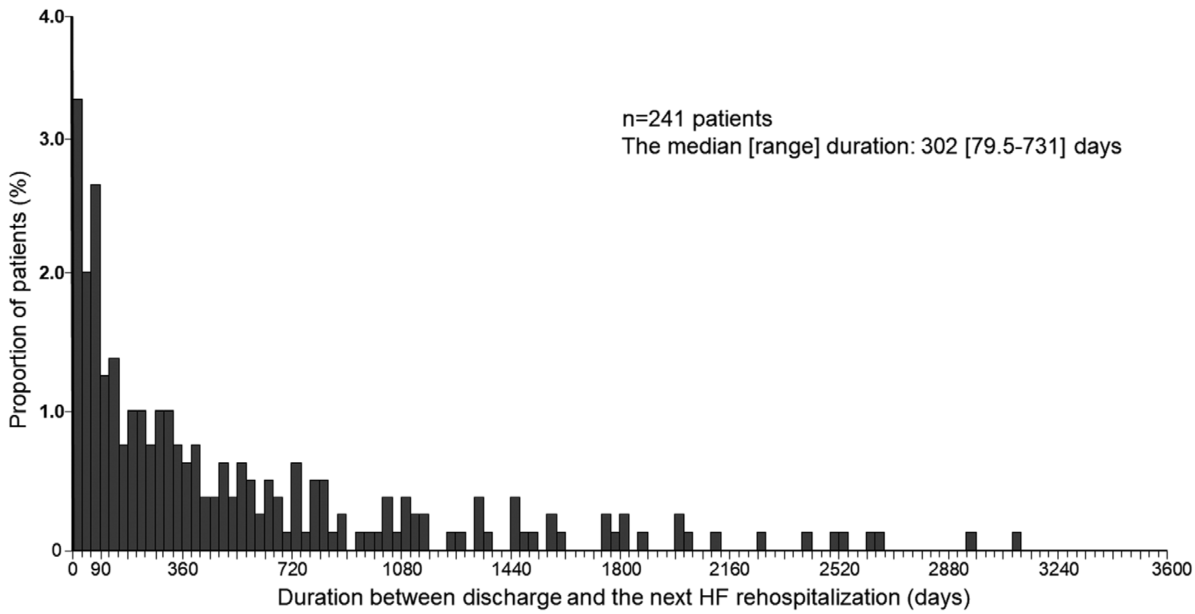

Figure 2. Proportion of patients re-admitted in each 30-day interval during the total follow-up period from discharge to rehospitalization for HF among the total population (n=241 patients). The median duration between discharge from the index HF hospitalization and the next unplanned HF rehospitalization was 302 [79.5–731] days. HF, heart failure.

median [25–75th interquartile range] length of hospital stay was 19 [13–29] days. The mean LVEF at discharge was 45.9±16.6%, and the median level of BNP at discharge was 251 [132–486] pg/mL. The median follow-up period, from the day of discharge, was 895 [428–1,806] days.

Timing of re-HHF

There were 241 patients (30.8%) who were re-admitted for HF, and the median duration between discharge from the index HF hospitalization and the next unplanned HF rehospitalization was 302 [79.5–731] days.

As shown in **Figure 2**, the incidence of re-HHF was the highest in the first 30 days after discharge (3.3% [26 patients] of the total population). Meanwhile, approximately 25% of the patients with re-HHF were re-admitted within 90 days, which corresponded to 8.0% (63 patients) of the total population. At 90 days after the first discharge, the number of patients with re-HHF decreased sharply and tended to decrease over time. A focused analysis on the first 30-day interval divided into 5-day increments showed that only a few patients were re-admitted immediately after discharge, and almost 50% of the patients with 30-day re-HHF were re-admitted in the last 5-day interval of the 30-day period (**Figure 3**).

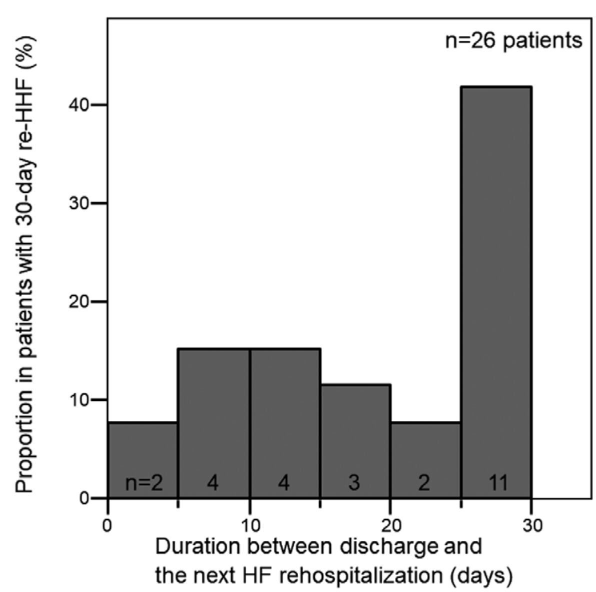

Figure 3. Proportion of patients re-admitted in each 5-day interval during the first 30 days after discharge among the patients with re-HHF within 30 days of discharge (n=26 patients). re-HHF, rehospitalization for heart failure.

Baseline Characteristics of Patients With 90-Day re-HHF

From the histogram pattern of the re-HHF rate in the present study, we noted that the first 90 days after discharge was a vulnerable period. Therefore, we compared the characteristics of the patients with 90-day re-HHF to those without 90-day re-HHF or 90-day death (**Table 1**). There were significantly more males, and renal function on admission and at discharge was significantly worse in the 90-day re-HHF group than in the without 90-day re-HHF or 90-day death groups. The other covariates, except for the CRP level on admission, were similar between groups.

Poor Prognosis in Patients With 90-Day re-HHF

During the median post-discharge follow-up period of 895

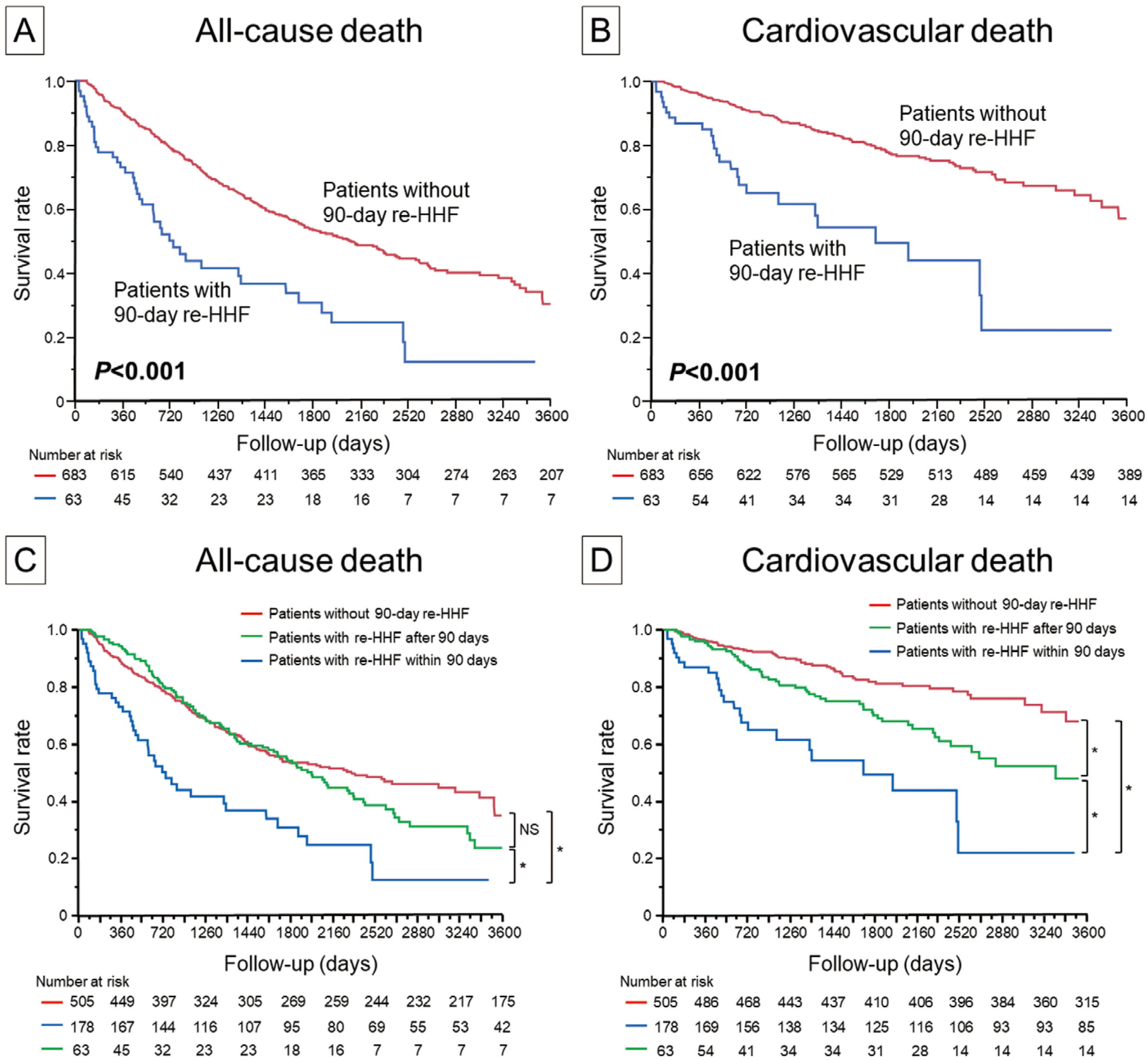

Figure 4. Kaplan-Meier event-free survival curves for all-cause death (**A**) and cardiovascular death (**B**) in patients with 90-day re-HHF (blue line, n=63) compared with patients without 90-day re-HHF (red line, n=683). Kaplan-Meier event-free survival curves for all-cause death (**C**) and cardiovascular death (**D**) in patients without re-HHF (red line, n=505), with re-HHF within 90 days (blue line, n=63) and with re-HHF after 90 days (green line, n=178). *P<0.001. NS, not significant; re-HHF, rehospitalization for heart failure.

[428–1,806] days, the rate of all-cause and cardiovascular death was 44.2% (n=330 patients) and 19.3% (n=144 patients), respectively. As shown in **Figure 4A**,**B**, the Kaplan-Meier curves were significantly distinct between patients with and without 90-day re-HHF for all-cause death (log-rank P<0.001) and cardiovascular death (log-rank P<0.001). The unadjusted HR suggested a significant association of all-cause death (HR 2.321, 95% CI 1.654–3.174; P<0.001) and cardiovascular death (HR 3.396, 95% CI 2.153–5.145; P<0.001) with 90-day re-HHF (**Table 2**). These findings remained significant even after adjustment for covariates in the multivariate Cox proportional hazard models (**Table 2**), showing that the patients with 90-day re-HHF had worse prognoses than those without 90-day re-HHF.

When we divided the patients into 3 groups (without re-HHF (n=505), with re-HHF within 90 days (n=63) and with re-HHF after 90 days (n=178)), the Kaplan-Meier curves of cardiovascular death differed significantly (log-rank P<0.001). For all-cause death, the Kaplan-Meier curves of patients with re-HHF within 90 days vs. with re-HHF after 90 days; and those with re-HHF within 90 days vs. those without re-HHF differed significantly (log-rank P<0.001). However, patients without re-HHF and those with re-HHF after 90 days did not differ significantly (log-rank P=0.314) (**Figure 4C**,**D**).

Table 2. Cox Regression Analysis of 90-Day re-HHF for Adverse Outcomes

	All-cause death			Cardiovascular death		
	HR	95% CI	P value	HR	95% CI	P value
Unadjusted	2.321	(1.654–3.174)	<0.001	3.396	(2.153–5.145)	<0.001
Adjusted model 1	2.187	(1.556–2.995)	<0.001	3.188	(2.016–4.847)	<0.001
Adjusted model 2	2.048	(1.405–2.897)	<0.001	3.210	(1.975–5.009)	<0.001
Adjusted model 3	2.053	(1.407–2.908)	<0.001	3.241	(1.991–5.065)	<0.001
Adjusted model 4	2.094	(1.434–2.968)	<0.001	3.277	(2.011–5.126)	<0.001
Adjusted model 5	1.973	(1.346–2.807)	<0.001	3.188	(1.949–5.011)	<0.001
Adjusted model 6	2.039	(1.376–2.936)	<0.001	3.610	(2.181–5.759)	<0.001
Adjusted model 7	2.137	(1.427–3.106)	<0.001	4.015	(2.412–6.451)	<0.001

Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, levels of hemoglobin, eGFR, and BNP at discharge. Model 3, adjusted for age, sex, levels of hemoglobin, eGFR, and BNP at discharge, SBP; and heart rate. Model 4, adjusted for age, sex, levels of hemoglobin, eGFR, and BNP at discharge, SBP, heart rate, and LVEF. Model 5, adjusted for age, sex, and levels of hemoglobin, eGFR, and BNP at discharge, SBP, heart rate, LVEF, diabetes mellitus, and AF. Model 6, adjusted for age, sex, hemoglobin, eGFR, BNP, SBP, heart rate, LVEF, diabetes mellitus, AF, causes of HF. Model 7, adjusted for age, sex, hemoglobin, eGFR, BNP, SBP, heart rate, LVEF, diabetes mellitus, AF, causes of HF, and medications at discharge. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Table 3. Predictors of 90-Day re-HHF

Covariate	90-day re-HHF					
	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (per 1 year)	1.015	(0.994–1.038)	0.170	1.014	(0.992–1.038)	0.205
Male/female	1.677	(1.005–2.884)	0.048	1.746	(1.036–3.031)	0.036
Length of hospitalization (days)	1.000	(0.984–1.008)	0.949			
Discharged home/Transfer	1.730	(0.712–5.701)	0.250			
Diabetes mellitus	1.490	(0.908–2.466)	0.115			
AF	1.258	(0.742–2.082)	0.386			
Vital signs on admission						
Heart rate (per 1 beat/min)	0.997	(0.988–1.006)	0.486			
SBP (per 10 mmHg)	0.987	(0.920–1.056)	0.703			
Vital signs at discharge						
Heart rate (per 1 beat/min)	0.991	(0.969–1.013)	0.437			
SBP (per 10 mmHg)	1.010	(0.996–1.023)	0.163			
LVEF at discharge (per 1%)	1.007	(0.992–1.022)	0.386			
Laboratory data on admission						
BNP (per 100 pg/mL)	0.999	(0.972–1.021)	0.925			
Hemoglobin (per 1 g/dL)	0.935	(0.843–1.035)	0.196			
BUN (per 1 mg/dL)	1.007	(0.996–1.017)	0.174			
eGFR (per 1 mL/min/1.73 m^2)	0.989	(0.980–0.999)	0.025	0.999	(0.979–1.020)	0.938
Laboratory data at discharge						
BNP (per 100 pg/mL)	1.020	(0.969–1.055)	0.389			
Hemoglobin (per 1 g/dL)	0.915	(0.806–1.033)	0.152			
BUN (per 1 mg/dL)	1.016	(1.004–1.026)	0.009	1.011	(0.995–1.026)	0.172
eGFR (per 1 mL/min/1.73 m^2)	0.988	(0.977–0.998)	0.021	0.995	(0.969–1.019)	0.708
Medications at discharge						
β-blocker (%)	1.062	(0.645–1.780)	0.814			
ACEI/ARB (%)	0.854	(0.431–1.945)	0.685			
MRA (%)	0.757	(0.427–1.284)	0.309			
Loop diuretic (%)	1.264	(0.698–2.485)	0.455			

Abbreviations as in Tables 1,2.

Table 4. Predictors of 90-Day Death

Covariate	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (per 1 year)	1.056	(1.024–1.092)	<0.001	1.042	(1.007–1.078)	0.018
Male/female	1.760	(0.947–3.431)	0.074			
Length of hospitalization (days)	1.006	(0.997–1.012)	0.145			
Diabetes mellitus	1.504	(0.826–2.778)	0.182			
AF	1.572	(0.845–2.865)	0.150			
Heart rate at discharge (per 1 beat/min)	1.040	(1.016–1.063)	0.002	1.037	(1.013–1.062)	0.003
SBP at discharge (per 10 mmHg)	0.866	(0.726–1.027)	0.098			
LVEF at discharge (per 1%)	0.999	(0.981–1.018)	0.943			
BNP at discharge (per 100 pg/mL)	1.050	(1.013–1.077)	0.011	1.042	(1.005–1.081)	0.024
Hemoglobin at discharge (per 1 g/dL)	0.778	(0.656–0.913)	0.002	0.870	(0.716–1.057)	0.161
BUN at discharge (per 1 mg/dL)	1.022	(1.009–1.033)	0.002	1.011	(0.995–1.026)	0.181
eGFR at discharge (per 1 mL/min/1.73 m²)	1.000	(0.988–1.011)	0.992			
β-blocker (%)	1.801	(0.950–3.649)	0.072			
ACEI/ARB (%)	0.383	(0.199–0.798)	0.012	0.847	(0.384–2.060)	0.699
MRA (%)	0.900	(0.462–1.672)	0.744			
Loop diuretic (%)	1.304	(0.637–3.024)	0.487			

Abbreviations as in Tables 1,2.

Predictors of 90-Day re-HHF

Because patients with 90-day re-HHF were found to have poor prognoses, we examined the predictors for 90-day re-HHF to identify patients at high risk (**Table 3**). In the multivariate analysis that included age as a well-known strong prognostic factor of HF, male sex (HR 1.750, 95% CI 1.042–3.029; P=0.034) remained an independent predictor of 90-day re-HHF. Any other covariates, including length of hospital stay and place of stay after discharge, were not associated with 90-day re-HHF in either univariate or multivariate analyses. Of the variables measured on admission, eGFR was the only statistically significant predictor of 90-day re-HHF in the univariate analysis, but the association between eGFR and 90-day re-HHF was not statistically significant in the multivariate analysis.

Predictors of 90-Day Death

Next, we investigated the predictors of 90-day death to investigate similarities between patients with 90-day re-HHF and 90-day death. There were 6 patients who were re-admitted for HF and died within 90 days and 37 patients who died within 90 days without re-HHF. A total of 43 patients were included in the analysis (**Figure 1**). The various causes of death among the 37 patients who died within 90 days without re-HHF included sudden death, cancer, infection, hemorrhage, acute myocardial infarction, multiple organ failure, and cerebral infarction. Patients who died within 90 days were older and had lower BMI than those without 90-day re-HHF or 90-day death. Heart rate and the levels of BNP, BUN, and C-reactive protein at discharge were higher, and the hemoglobin level was lower in patients who died within 90 days. Meanwhile, other covariates were similar in both groups except for the proportion of patients treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers at discharge (**Supplementary Table 1**). In the multivariate analysis, the independent predictors of 90-day death were age (HR 1.042, 95% CI 1.007–1.078; P=0.018), heart rate (HR 1.037, 95% CI 1.013–1.062; P=0.003), and BNP level (HR 1.042, 95% CI 1.005–1.081; P=0.024) at discharge (**Table 4**). These are all well-known conventional risk factors of HF and were different from the predictors of 90-day re-HHF.

Discussion

The present study demonstrated that the incidence of re-HHF was the highest in the first 30 days after discharge and remained high until 90 days, after which it started to markedly decrease. This finding is consistent with the concept that among patients with HF, there is a vulnerable phase for rehospitalization immediately after discharge until 2–3 months later.[20–22] The incidence of 30-day re-HHF (3.3%) in the present study was much lower than that reported in the USA (3.3% vs. 20–25%), and the incidence of 90-day re-HHF was only 8.0%. The 30-day re-HHF rate in the present study was also lower than that in ASCEND-HF (5.0%)[11] or EVEREST (5.6%),[12] which were large, global, randomized clinical trials that enrolled acute HF patients from countries other than Japan. The proportion of patients with NYHA class 3 or 4 in the ASCEND-HF and the ATTEND registries was approximately 62% and 81.4%, respectively.[11,23] On the other hand, in the present study, 89.8% of the patients were graded as NYHA class 3 or 4 on admission. Even though the present study included more severe HF patients than the other studies, the incidence of 30-day re-HHF was relatively low.

The marked difference in the incidence of 30-day or 90-day re-HHF cannot be explained easily because many factors, including medical factors, socioeconomic factors, and insurance systems are related to early re-HHF. Short hospital stay has been recently reported to be associated with early re-HHF.[24] Country-level mean length of hospital stay ranged from 4.9 to 14.6 days in ASCEND-HF,[16] and overall median length of hospital stay across all regions was 8 [4–11] days in the EVEREST trial.[12] The subanalyses of the incidence of re-HHF reported in those 2 studies also indicated shorter length of hospital stay was closely related to higher rate of 30-day re-HHF. The lower rate of 30- or 90-day re-HHF in the present study may be partly attributed to longer hospital stay (19 days). However, another multicenter cohort study conducted in Canada indicated a non-linear, U-shaped correlation between length of hospital stay and 30-day re-HHF; that study reported that 5–6 days in hospital yielded the lowest risk for 30-day re-HHF.[25] Moriyama et al also reported that shorter length of stay was associated with increased rates of 30-day HF readmission while longer length of stay also showed the same trend in Japan.[26] Therefore, factors other than the length of hospital stay should be taken into consideration.

In this study, only 11.5% of the patients with 30-day re-HHF were re-admitted by day 7, which was much lower than reported in the ASCEND-HF trial (31.3%).[11] In PROTECT, with respect to 30-day readmissions for HF, the rate increased approximately 1 week after the initial discharge.[27] Overall, 30-day re-HHF might not be associated only with the length of hospital stay, but very early re-HHF within 7 days after discharge could be related to the length of hospital stay because the patients might not be treated sufficiently.

To the best of our knowledge, the present study is the first to report a predominant effect of 90-day re-HHF on long-term outcomes. The patients with 90-day re-HHF had worse prognoses than those without 90-day re-HHF. Even when we divided the patients into 3 groups (without re-HHF, with re-HHF within 90 days and with re-HHF after 90 days), the patients with 90-day re-HHF had the worst prognosis among these groups. This suggested that once patients were re-admitted to hospital for HF within 90 days after discharge, they would have a significantly worse prognosis than other patients, including patients with re-HHF after 90 days. From this point of view, to improve the prognoses of ADHF it is important to identify patients at risk of readmission within 90 days after discharge. Predictive factors of 30-day re-HHF reported in previous studies included congestion at admission, renal function, and BNP.[27,28] However, in the present study, none of these parameters was associated with 90-day re-HHF. We also assessed the other parameters on admission and at discharge, but there was no association with 90-day re-HHF. Unexpectedly, male sex was identified as an independent predictor. The stratified analysis according to sex revealed that more male patients than female were discharged home (**Supplementary Table 2A**), which may partially explain why male sex was associated with a higher 90-day re-HHF (i.e., they could be re-admitted to hospital because they were discharged home). Although the precise reason why males were at higher risk for 90-day re-HHF was not elucidated from the present study, culturally, elderly Japanese males are not usually well self-controlled or can manage living alone compared with elderly Japanese females.

In addition, we compared the predictors of 90-day re-HHF with those of 90-day death and found that they were different. The risk factors of 90-day death were old age, high heart rate, and high levels of BNP at discharge, which were all well-known conventional prognostic factors for HF,[29,30] and were not the same as for 90-day re-HHF (i.e., male sex). Because there were some patients with non-cardiovascular 90-day deaths, comorbidities may have affected the estimates. However, the risk factors of 90-day death in the present study were similar to the conventional risk factors for HF, which suggests that severe HF results in cardiovascular death, but early re-HHF does not. Therefore, clinicians should recognize that the predictors of 90-day re-HHF are not related to the clinical risk factors of HF. Further, new approaches, such as patient and family education, discharge planning, and multidisciplinary care should be considered. Further large-scale studies are needed to determine the optimal preventive approach for re-HHF.

Furthermore, we also examined the determinants of a composite outcome that combined all-cause death and re-HHF. In multivariate analysis, the independent predictors of 90-day all-cause death or HF rehospitalization were age (HR 1.026, 95% CI 1.004–1.048; P=0.021), male sex (HR 1.966, 95% CI 1.242–3.179; P=0.004), and BUN level (HR 1.013, 95% CI 1.001–1.025; P=0.038) at discharge (**Supplementary Table 3**).

Study Limitations

First, this was a single-center study with a relatively small number of ADHF patients. Second, it was a retrospective analysis of prospectively collected data. Third, the study population was limited to Japanese patients. Finally, the predictors of 90-day re-HHF and death were not directly compared statistically.

Conclusions

The present study demonstrated that the majority of re-HHF cases in Japan occur within 90 days of discharge, but the incidence was much lower than that in the West. Longer length of hospital stay might be related to the lower rate of early re-HHF during the first 30 days after discharge in Japan. Other than male sex, the predictors of 90-day re-HHF were not well-known prognostic factors of HF and were essentially different from those of 90-day all-cause death. These findings might provide new insight into the optimal management of HF to prevent re-HHF.

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Conflicts of Interest

None declared.

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Supplementary Files

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