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ORIGINAL RESEARCH

Prognostic Implications of Early and Midrange Readmissions After Acute Heart Failure Hospitalizations: A Report From a Japanese Multicenter Registry

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BACKGROUND: Although 30-day readmission is thought to be an important quality indicator in patients with hospitalized heart failure, its prognostic impact and comparison of patients who were readmitted beyond 30 days has not been investigated. We assessed early (0–30 days) versus midrange (31–90 days) readmission in terms of incidence and distribution, and elucidated whether the timing of readmission could have a different prognostic significance.

METHODS AND RESULTS: We examined patients with hospitalized heart failure registered in the WET-HF (West Tokyo Heart Failure) registry. The primary outcomes analyzed were all-cause death and HF readmission. Data of 3592 consecutive patients with hospitalized heart failure (median follow-up, 2.0 years [interquartile range, 0.8–3.1 years]; 39.6% women, mean age 73.9±13.3 years) were analyzed. Within 90 days after discharge, HF readmissions occurred in 11.1% patients. Of them, patients readmitted within 30 and 31 to 90 days after discharge accounted for 43.1% and 56.9%, respectively. Independent predictors of 30- and 90-day readmission were almost identical, and after adjustment, readmission for HF within 90 days (including both early and midrange readmission) was an independent predictor of subsequent all-cause death (hazard ratio, 2.36; $P<0.001$). Among 90-day readmitted patients, the time interval from discharge to readmission was not significantly associated with subsequent all-cause death.

CONCLUSIONS: Among patients readmitted within 90 days after index hospitalization discharge, ≈60% of readmission events occurred beyond 30 days. Patients readmitted within 90 days had a higher risk of long-term mortality, regardless of the temporal proximity of readmission to the index hospitalization.

Key Words: early readmission ■ heart failure ■ Hospital Readmission Reduction Program ■ outcome

Readmission within 30 days after a heart failure (HF) hospitalization is both a recognized indicator for disease progression and a source of considerable financial burden to the healthcare system.[1,2] Consequently, the identification of patients at risk for 30-day readmission is recognized as a key step in improving disease management and patient outcome,[3,4] although controversy remains in its implementation.[5–7] First, few studies investigated the impact of early readmission among patients with HF outside of Western countries,[8] despite the regional differences in HF management and healthcare system organization.[9] Second, the clinical impact of HF readmission on a 30-day postdischarge period and beyond has been scarcely investigated; the vulnerable period after discharge is considered to continue for 2 to 3 months after discharge, and "30-day" could be an arbitrary cutoff that is not supported by the pathophysiologic rationale related to HF.[10] This is an important hypothesis to investigate given a recent increase in postdischarge

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CLINICAL PERSPECTIVE

What Is New?

- Our data show that, among 90-day readmitted patients with heart failure, ≈60% patients readmitted beyond 30 days after discharge in a contemporary Japanese hospitalized heart failure registry.
- Readmission within 90 days after discharge was associated with subsequent all-cause death, but its timing (1–30 days versus 31–90 days) was not.

What Are the Clinical Implications?

- Not only 30-day readmission but also readmission within 90 days after discharge could be perceived as an alarming sign of subsequent worse prognosis in patients with hospitalized heart failure.
- Present readmission monitoring programs in which 30-day readmission has been used as a quality benchmark could be shortsighted, as the actual time window of the vulnerable period for readmission extends beyond 30 days.

Nonstandard Abbreviations and Acronyms

ATTEND	Acute Decompensated Heart Failure Syndromes
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan
GWTG-HF	Get With The Guidelines-Heart Failure
HF	heart failure
HHF	hospitalized heart failure
HR	hazard ratio
LVEF	left ventricular ejection fraction
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure
RAS	renin-angiotensin system
REALITY-AHF	Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure
SBP	systolic blood pressure
SHFM	Seattle Heart Failure Model
WET-HF	West Tokyo Heart Failure

mortality in patients with HF.[11] Indeed, a recent post hoc analysis of a large-scale clinical trial revealed that HF readmission for worsening of symptoms and/or signs resulting in augmentation or new administration of HF therapies continued beyond 30 days after patient discharge.[12] Given the continued risk of readmissions beyond the 30-day period, more recent episode payment models have shifted the focus from 30- to 90-day readmission for the management of patients with acute myocardial infarction.[13]

Accordingly, we investigated: (1) the incidence, distribution, predictors, and prognostic impact of readmission 0 to 30 and 31 to 90 days after index hospitalization discharge in Japan, and (2) whether the timing of readmission (early [0–30 days] versus midrange [31–90 days]) could have prognostic significance among the patients with hospitalized HF (HHF).

METHODS

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

Details of the WET-HF (West Tokyo Heart Failure) registry have been previously described.[14,15] Briefly, this database is a prospective, multicenter cohort registry designed to collect data pertaining to the clinical backgrounds and outcomes of patients hospitalized with acute HF who met the Framingham criteria for HF[16] as the primary cause of admission. Before the launch of this registry, information on the objective of the present study, its social significance, and an abstract were provided for clinical trial registration to the University Hospital Medical Information Network of Japan (UMIN000001171). The present study was conducted at 3 university hospitals and 3 tertiary referral hospitals within the metropolitan Tokyo area. To obtain a robust assessment of the care and patient outcomes, baseline data and outcomes were collected by dedicated clinical research coordinators from medical records and interviews with treating physicians. Data were entered into an electronic data-capturing system with a robust data query engine and system validations for data quality; outliers in the continuous variables or unexpected values in the categorical variables were selected by established criteria, and the originating institution was notified to verify the value. Moreover, the quality of the reporting was also verified by principal investigators (Y.S. and S.K.) at least once a year, and periodic queries were conducted to ensure its quality. Patients who refused to participate in the study or presented with concurrent HF and acute coronary syndrome were excluded from the registration. The study protocol was approved by the institutional review boards at each site, and research was conducted in accordance with the Declaration of Helsinki. Written or

oral informed consent was obtained from each patient before the study.

Data of 4000 consecutive patients with HHF registered in the WET-HF registry between 2006 and 2017 were analyzed. Figure 1A shows a flowchart describing the study design. Of the 4000 patients included in this cohort, 164 patients with in-hospital death and 244 patients without recorded follow-up information were excluded. After exclusion, data of 3592 patients who were stably discharged after index hospitalization were analyzed.

Definitions of Outcomes and Variables

Following discharge, a survey was performed using chart or telephone review. The following information regarding specific outcomes was obtained from participating cardiologists and investigators: (1) all-cause

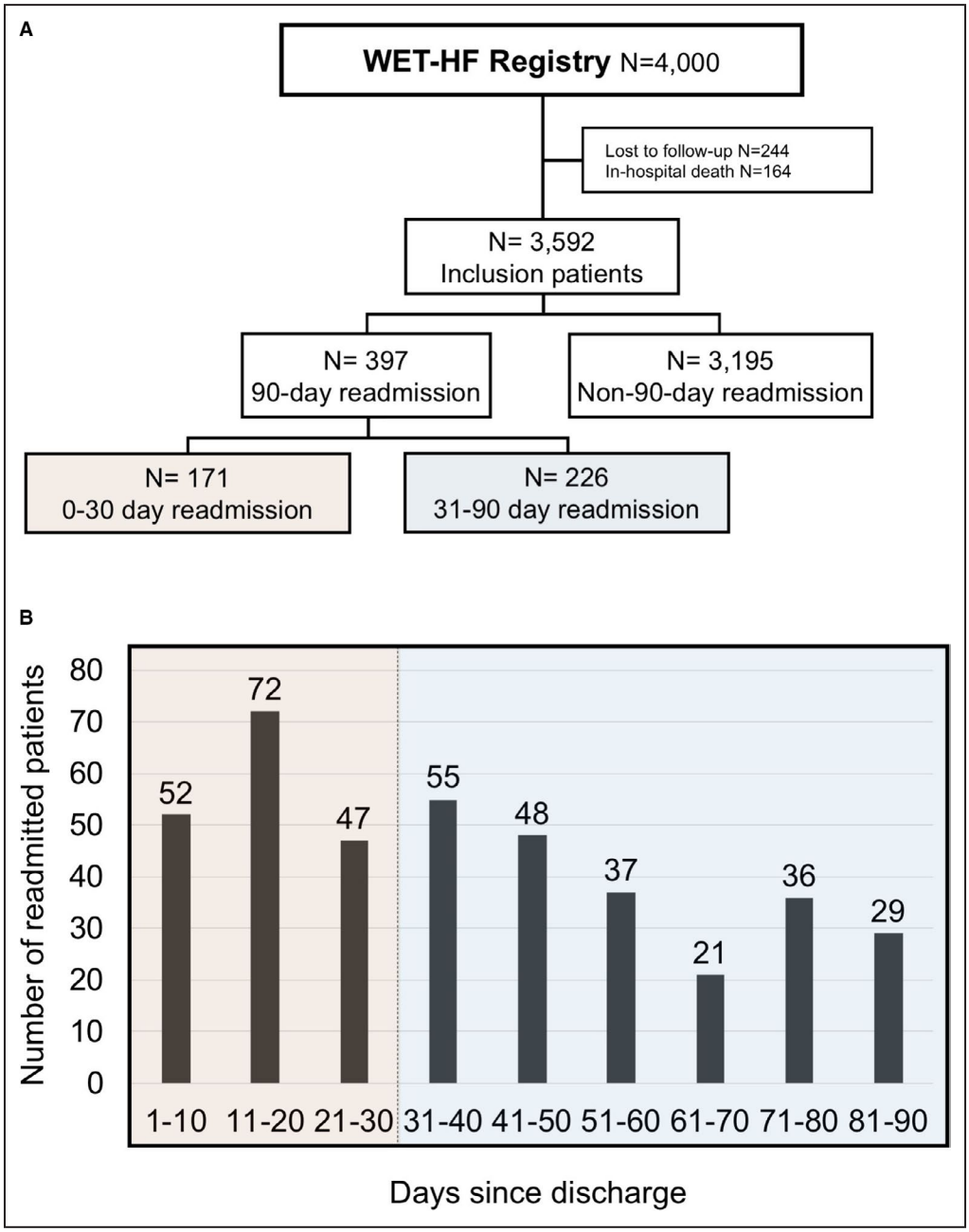

Figure 1. The study design and time distribution of 90-day readmission.
A, Flowchart describing the study design from the WET-HF (West Tokyo Heart Failure) registry. Patients were divided into 2 groups according to the presence of 90-day readmission. Ninety-day readmission groups were subdivided into 2 groups according to the timing of readmission (early [0–30 days] vs midrange [31–90 days]). **B**, Time distribution of 90-day readmission after discharge of index hospitalization.

death, and (2) HF readmission. Our registry obtained HF-specific readmission information in order to elucidate the clinical significance exclusively focusing on HF readmission. Regarding HF readmission, treating physicians at each participating hospital made decisions according to the usual standard of care. Since non-HF readmissions can involve noncardiac factors (eg, psychological, social, and environmental factors),[3] they were not considered to be the primary end point of the present analysis. Follow-up survey using a chart or telephone review was performed, and the date of index hospitalization discharge, HF rehospitalization, and mortality were properly collected and confirmed by site investigators and dedicated clinical research coordinators. The data acquisition rate for follow-up clinical events (eg, HF-related readmission and mortality) was 93.9%. Patients lost to follow-up were censored at the date of last contact.[17]

For the present analysis, the patients were further divided into 2 groups according to the presence or absence of HF readmission within 90 days after discharge from index HF hospitalization (90-day readmission and non–90-day readmission groups; Figure 1A). Then, the patients readmitted within 90 days were subdivided into 2 groups according to the readmitted time interval (early [0–30 days] and midrange [31–90 days] groups). The primary end point of this study was all-cause death. Prognostic impact of 90-day readmission (versus no 90-day readmission) as well as 0-30 days readmission (versus 31–90 days) during 2 years of follow-up was investigated. Time to all-cause mortality was defined as the time elapsed between the day of hospital discharge of the index hospitalization and the date of death. Patients who died before 30 days (or 90, 120, 180, 360 days) after discharge following index hospitalization were included in this study, not censored.

The Seattle Heart Failure Model (SHFM) score to predict annual all-cause mortality was calculated in accordance to the statistical model described in the original and our previous articles.[18,19] All laboratory data were evaluated at discharge, except for the percentage of lymphocytes, which was evaluated during the course of hospitalization. As Table S1 demonstrates, overall missing data were ≤5%, with the exception of SHFM score (20.8%) mainly because of lack of laboratory values such as total cholesterol and lymphocytes. These missing values were imputed as follows: (1) for variables pertaining to medication and device therapy, missing data were imputed to "no"; (2) for New York Heart Association class, missing data were imputed to "II" based on the frequency (class II; 63.1%) in the entire cohort; (3) for body weight, missing values were imputed to the sex-specific median; and (4) for systolic blood pressure (SBP), left ventricular ejection fraction (LVEF), total cholesterol, and percentage of lymphocytes, missing values were imputed to the median values of the entire cohort. These imputation rules have been previously shown to yield results similar to those obtained with multiple imputation methods.[4,20]

Statistical Analysis

Continuous variables were expressed as mean±SD for normally distributed variables as well as median with interquartile range for non-normally distributed variables (length of stay, SHFM score, and laboratory data that included uric acid, serum urea nitrogen, brain natriuretic peptide, lymphocyte, and total cholesterol). Categorical variables were expressed as percentages. Student *t* test or Mann–Whitney *U* test were used to compare normally or non-normally distributed variables, and Pearson chi-square test was used to compare categorical variables. The Cox proportional hazard model was used to analyze the determinants of 30- and 90-day readmission. Kaplan–Meier method was used to evaluate the impact of the readmission or its timing on subsequent all-cause death, and the calculation of the follow-up period began from the date of discharge of index hospitalization for both readmission and non-readmission groups; time-to-readmission interval and length of stay during readmission were included in the follow-up periods in the readmission groups. To evaluate the impact of readmission within 90 days on long-term death beyond 90 days, we conducted the landmark analysis at 90 days. Furthermore, to verify the timing of readmission that has no effect on survival rate, we analyzed the prognostic impact of readmission based on further timeline (ie, 120, 180, and 360 days) from initial discharge. In multivariate Cox proportional hazards models for predicting 30- or 90-day readmission, the models were adjusted for age, sex, previous HF admission, SBP, estimated glomerular filtration rate, sodium level, hemoglobin level, LVEF, and β-blocker, renin-angiotensin system (RAS) inhibitor, and mineralocorticoid receptor antagonist use. For readmission outcomes, death was assumed to be a competing risk; thus, we additionally performed Fine and Gray analysis. Further, for predicting all-cause death, variables of "90-day readmission" were added. For all statistical analyses, statistical significance was accepted at $P<0.05$. Data analysis was performed using SPSS 24.0 for Windows (IBM) except for Fine and Gray analysis, which was performed using R 3.4.2 (The R Foundation).

RESULTS

Of 3592 patients with HHF (39.6% women; mean age, 73.9±13.3 years), 397 patients (11.1%) were readmitted within 90 days after discharge (90-day readmission group). The median follow-up period

of the survivors was 2.0 years (interquartile range, 0.8–3.1 years), and the median time of HF readmission was 34 days (interquartile range, 16–58 days) after the discharge from index HF hospitalization. Overall, 171 patients (43.1% of readmitted patients within 90 days) had been readmitted within 30 days after discharge, and 226 patients (56.9% of readmitted patients within 90 days) had been readmitted 31 to 90 days after discharge (Figure 1B).

The characteristics of patients with and without 90-day readmission in the overall cohort are summarized in Table 1. Patients who were readmitted within 90 days were more frequently women of older age with lower body mass index, hemoglobin level, and estimated glomerular filtration rate, and had a higher prevalence of ischemic cardiomyopathy and previous HF admission than non–90-day readmitted patients. In addition, 90-day readmitted patients had higher SHFM scores. Multivariate analysis showed that previous HF admission (hazard ratio [HR], 1.73; 95% CI, 1.40–2.13), older age (HR, 1.02; 95% CI, 1.01–1.03), lower SBP (HR, 0.99; 95% CI, 0.98–1.00), lower hemoglobin level (HR, 0.88; 95% CI, 0.83–0.93), lower LVEF (HR, 0.99; 95% CI, 0.98–0.99), and nonuse of RAS inhibitors (HR, 0.68; 95% CI, 0.56–0.84) were independent determinants of 90-day readmission (Table 2). The results persisted in the additional analysis for predicting 90-day readmission after accounting for competing risk of death for readmission outcome (Table S2). Independent determinants of 30-day readmission were similar to those of 90-day readmission including previous HF admission (HR, 1.98; 95% CI, 1.44–2.73), older age (HR, 1.02; 95% CI, 1.00–1.03), lower LVEF (HR, 0.98; 95% CI, 0.97–0.99), and nonuse of RAS inhibitors (HR, 0.53; 95% CI, 0.39–0.72) but also included nonuse of mineralocorticoid receptor antagonists (HR, 0.69; 95% CI, 0.49–0.98) (Table S3).

During a median follow-up of 2.0 years (interquartile range, 0.8–3.1 years), 122 (30.7%) and 461 (14.4%) patients died in the 90-day readmission and non–90-day readmission groups, respectively. Kaplan–Meier estimates demonstrated higher crude rates of all-cause mortality among patients with 90-day readmission in the overall cohort (Figure 2A). After adjustment, 90-day readmission remained an independent risk factor for all-cause death (HR, 2.36; 95% CI, 1.92–2.91) along with older age, male sex, lower SBP, estimated glomerular filtration rate, sodium level, hemoglobin level, LVEF, and nonuse of β-blockers and RAS inhibitors (Table 3). By a landmark analysis performed at 90 days after index hospitalization, 90-day readmission was associated with increased subsequent mortality both within and beyond 90 days of follow-up (Figure 2A). Furthermore, landmark analysis performed at 120, 180, and 360 days after index hospitalization revealed that each of the readmission timeframes was associated with an increased subsequent mortality, although the difference narrowed as the time interval from index hospitalization increased (Figure S1A through S1C).

We then subdivided the 90-day readmitted patients into 2 categories according to the timing of readmission: early (0–30 days) and midrange (31–90 days) readmission groups. No significant differences in patient characteristics were detected between these groups, except for the percentage of lymphocytes and prescription of loop diuretics and RAS inhibitors (Table 1). Further, the incidence of all-cause mortality did not differ between early and midrange readmission groups (Figure 2B). Among 90-day readmitted patients, multivariate analysis showed that older age, lower SBP, estimated glomerular filtration rate, sodium level, LVEF, and nonuse of β-blockers and RAS inhibitors were independently associated with all-cause death (Table 4).

DISCUSSION

The present study demonstrated the following key points: (1) among 90-day readmitted HF patients, 57% of patients were readmitted beyond 30 days after discharge; (2) independent predictors of 30- and 90-day readmissions were almost identical; (3) readmission within 90 days after discharge was associated with a higher risk for subsequent all-cause death but its timing (0–30 days versus 31–90 days) was not.

To date, several studies that investigated the impact of short-term (eg, 30-day) readmission on subsequent mortality have been reported. In the Alabama Heart Failure Project, a US registry created during an earlier era of HF management (1998–2002), all-cause mortality occurred more frequently in patients with compared with patients without 30-day all-cause readmission.[21] A Spanish study using linked administrative data also demonstrated that readmission at 30 days after HF hospitalization was associated with higher in-hospital mortality.[8] More recently, the continued incidence of HF readmissions beyond 30 days after discharge of index hospitalization has also been reported.[22,23] In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial,[12] 24% of readmissions occurred within the first 30 days after discharge, whereas 20% of them were within 31 to 60 days after discharge and 56% of them were beyond 60 days after discharge. Additionally, cumulative data from 3 trials with newly discharged patients with HHF also demonstrated that a high number of HF readmissions occurred beyond 30 days after discharge.[24,25] These findings, together with ours, support the perspective that present readmission monitoring programs (eg, Hospital Readmission Reduction Program, in which 30-day readmission has been used

Table 1. Baseline Characteristics

Variables	Overall Cohort			90-d Readmitted Patients		
	Non–90-d Readmission (n=3195)	90-d Readmission (n=397)	*P* Value	0 to 30 d (n=171)	31 to 90 d (n=226)	*P* Value
Demographics and medical history						
Age, y	73.5±13.5	76.7±11.7	<0.001	76.1±12.6	77.0±10.9	0.417
Men, %	61.1	54.4	0.010	52.6	55.7	0.536
Body mass index, kg/m^2	21.8±4.1	20.9±3.6	<0.001	20.7±3.7	21.0±3.6	0.465
Hypertension, %	65.7	67.5	0.478	69.0	66.4	0.579
Diabetes mellitus, %	33.6	37.3	0.146	36.8	37.6	0.875
Dyslipidemia, %	39.0	36.4	0.308	35.7	36.9	0.811
Atrial fibrillation, %	47.0	56.2	0.001	60.8	52.7	0.105
Chronic obstructive pulmonary disease, %	4.9	3.5	0.217	5.3	2.2	0.100
Chronic kidney disease, %	67.2	77.3	<0.001	74.3	79.6	0.205
Stroke, %	13.2	12.7	0.757	16.0	10.2	0.089
Cause of HF, %						
Ischemic	28.2	33.0	0.045	31.0	34.5	0.460
Dilated	14.6	10.6	0.032	10.5	10.6	0.976
Valvular	25.4	31.2	0.013	31.0	31.4	0.928
Previous HF admission, %	27.8	46.8	<0.001	48.2	45.6	0.628
New York Heart Association class at discharge, %			<0.001			0.665
I	16.2	11.3		11.1	11.6	
II	64.6	58.2		60.6	55.8	
III	18.0	27.5		24.7	29.9	
IV	1.2	3.0		3.6	2.7	
Vital signs at discharge						
Heart rate, beats per min	71.0±12.7	72.8±12.3	0.008	73.4±13.8	72.4±11.1	0.400
SBP, mm Hg	112.6±17.8	109.7±18.3	0.003	111.8±19.0	108.2±17.7	0.053
Echocardiographic parameters						
LVEF, %	44.8±15.2	43.0±15.8	0.026	43.1±16.4	42.7±15.5	0.776
Left atrial dimension, mm	44.7±9.1	46.1±10.3	0.006	45.5±8.9	46.5±11.2	0.400
Laboratory data at discharge						
Hemoglobin, g/dL	12.2±2.2	11.5±2.0	<0.001	11.7±2.0	11.3±2.0	0.121
Sodium, mEq/L	138.6±3.5	138.3±4.0	0.120	138.4±4.2	138.2±3.8	0.699
Potassium, mEq/L	4.3±0.5	4.3±0.6	0.828	4.3±0.6	4.4±0.5	0.139
Uric acid, mg/dL	6.8 (5.6–8.0)	6.8 (5.7–8.1)	0.790	6.8 (5.7–7.8)	6.8 (5.8–8.2)	0.874
Blood urea nitrogen, mg/dL	22.2 (16.4–31.6)	25.1 (18.2–35.5)	<0.001	24.9 (18.0–35.3)	25.2 (18.5–35.6)	0.631
Estimated glomerular filtration rate, mg/dL per 1.73 m^2	51.4±23.5	45.9±23.7	<0.001	46.3±23.3	45.7±24.1	0.808
Brain natriuretic peptide, pg/mL	237 (121–465)	450 (218–729)	<0.001	501 (259–958)	439 (192–629)	0.054
N-terminal pro–brain natriuretic peptide, pg/mL	1958 (1029–3817)	1906 (1340–5915)	0.720	3234 (1578–11 038)	1842 (1287–5846)	0.216
Lymphocyte, %	21.0 (15.6–27.2)	21.0 (15.0–27.0)	0.357	20.7 (13.5–24.5)	21.0 (15.7–27.4)	0.014
Total cholesterol, mg/dL	157.0 (137.0–179.0)	157.0 (136.4–176.5)	0.196	157.0 (136.8–177.0)	157.0 (137.0–179.0)	0.375
Medication or device therapy						
Loop diuretics, %	75.1	77.8	0.241	69.6	84.1	0.001
β-Blockers, %	76.6	77.1	0.839	76.6	77.4	0.846
RAS inhibitors, %	64.6	55.2	<0.001	48.5	60.2	0.021

(*Continued*)

Table 1. Continued

Variables	Overall Cohort			90-d Readmitted Patients		
	Non–90-d Readmission (n=3195)	90-d Readmission (n=397)	*P* Value	0 to 30 d (n=171)	31 to 90 d (n=226)	*P* Value
Mineralocorticoid receptor antagonists, %	34.9	33.3	0.537	28.1	37.2	0.062
Statins, %	35.1	34.5	0.801	36.3	33.2	0.524
Allopurinol, %	21.7	27.2	0.012	26.9	27.4	0.906
Implantable cardioverter-defibrillator, %	3.4	4.0	0.526	4.7	3.5	0.568
Cardiac resynchronization therapy, %	0.8	1.0	0.584	1.2	0.9	0.779
Length of stay, d	14 (10–23)	15 (10–22)	0.592	16 (9–25)	15 (11–22)	0.733
SHFM score	0.239 (–2.85 to 0.78)	0.542 (0.07–1.05)	<0.001	0.462 (0.016–1.03)	0.589 (0.078–1.10)	0.472

Data are shown as mean±SD or median with interquartile range or percentage. HF indicates heart failure; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system; SBP, systolic blood pressure; and SHFM, Seattle Heart Failure Model.

as a quality benchmark) could be shortsighted, as the actual time window of the vulnerable period for readmission extends beyond 30 days.[26,27] Recently, evolving concepts of value-based reimbursement have shifted the focus to 90-day readmission after hospital discharge. The substantial proportion of cost within 90 days of an acute myocardial infarction is estimated to be incurred from readmission, and the Centers for Medicare & Medicaid Services announced the implementation of a voluntary 90-day episode payment model for acute myocardial infarction.[13]

In addition, the impact of early readmission on subsequent death was manifested both within and beyond 90 days after index hospitalization based on our landmark analysis, and its impact was remarkable beyond 30 days. Further, the prognostic impact of readmission did not differ, regardless of the time from the index hospitalization, meaning that not only 30-day readmission but also the readmission within 90 days after discharge could be perceived as an alarming sign of subsequent worse prognosis in patients with HHF. These findings can have significant clinical implications for several reasons, especially for early-readmitted patients with HF. Because the prognostic impact of early readmission was not manifested within 30 days, this timeframe (within 30 days) could be an opportunity to implement shared decision-making (eg, individualized decision regarding device-based therapy and advanced care planning) and multidisciplinary patient educational programs with optimal medical therapy and strict adherence to recommended lifestyle modifications.

Table 2. Cox Proportional Hazard Analysis for Predicting 90-Day Readmission in the Overall Cohort

	HR	95% CI	*P* Value
Age	1.02	1.01–1.03	<0.001
Men	0.86	0.70–1.06	0.153
Previous HF admission	1.73	1.40–2.13	<0.001
SBP	0.99	0.98–1.00	0.002
Estimated glomerular filtration rate	1.00	0.99–1.00	0.161
Sodium	0.99	0.96–1.01	0.330
Hemoglobin	0.88	0.83–0.93	<0.001
LVEF	0.99	0.98–0.99	<0.001
β-Blockers	0.98	0.77–1.26	0.881
RAS inhibitors	0.68	0.56–0.84	<0.001
Mineralocorticoid receptor antagonists	0.88	0.71–1.10	0.266

HF indicates heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system; and SBP, systolic blood pressure.

Our study revealed that the incidence of readmission within 30 days and 90 days were 4.8% and 11.1%, respectively. The incidence of early HF readmission in Japan has been reported to be low compared with that in Western countries; around 5% (30-day) in 3 large-scale quality acute HF registries (ATTEND [Acute Decompensated Heart Failure Syndromes], REALITY-AHF [Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure], and WET-HF)[23] and 3.3% (30-day) and 8.0% (90-day) in the most recently published data from a single university hospital,[28] which were consistent with our data. The incidence of 30-day HF readmission in Western countries was around 10% to 20% in OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) and the GWTG-HF (Get With The Guidelines-Heart Failure) registry.[29–31] The precise reason for the lower early readmission rates in Japan remains unclear. However, a relatively longer length of hospital stay, a well-known determinant of readmission outcomes,[32,33] could contribute to the lower incidence

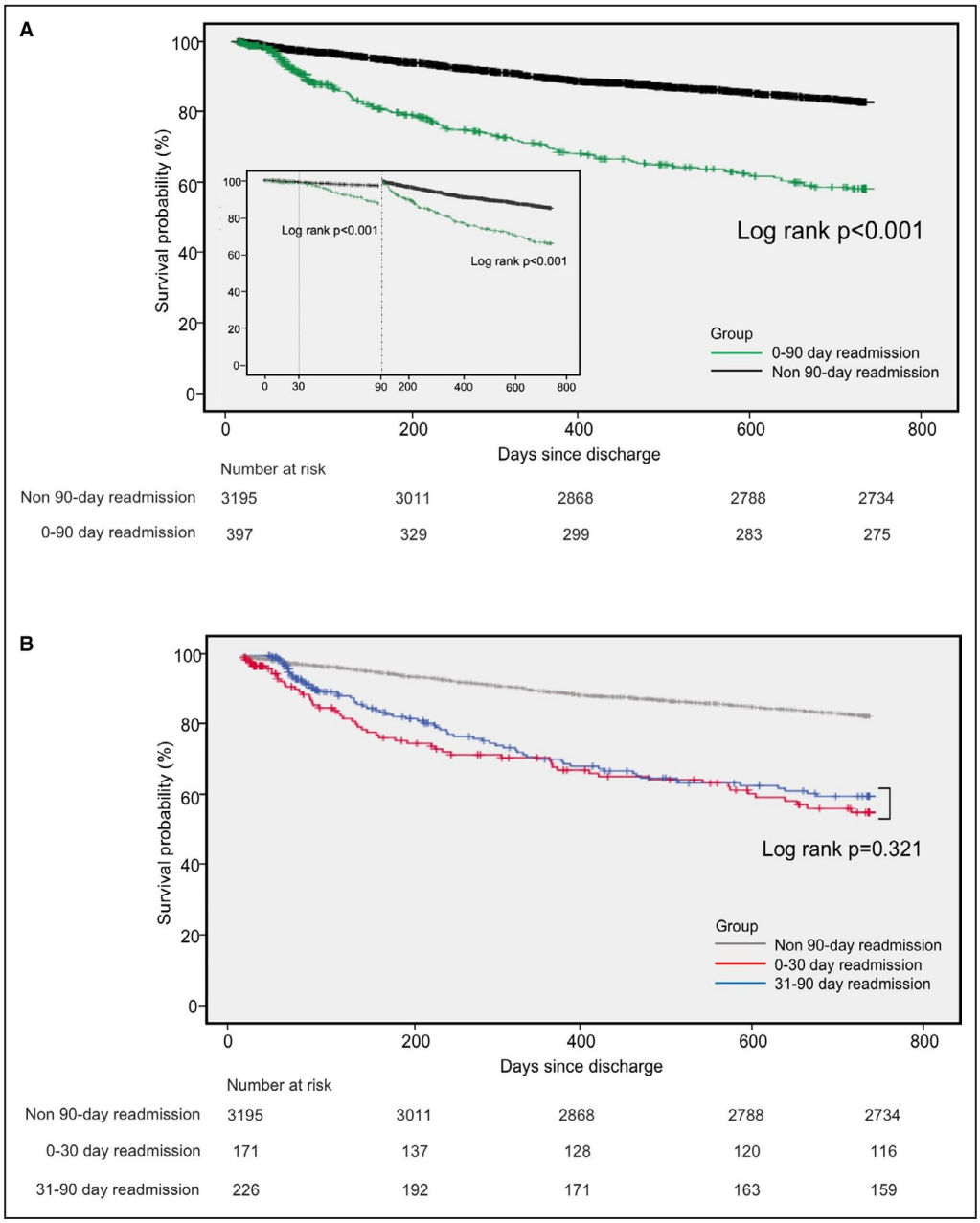

Figure 2. Kaplan–Meier analysis demonstrating survival rate of 90-day readmission.
A, Kaplan–Meier analysis demonstrating survival rate of 90-day readmitted patients and non–90-day readmitted patients in 2-year-follow-up with landmark analysis at 0 and 90 days. **B**, Comparison of all-cause death outcome between 0- to 30-day readmission vs 31- to 90-day readmission vs non–90-day readmission demonstrated by Kaplan–Meier analysis.

of HF readmissions in Japanese patients with HF. For instance, longer length of stay could be associated with sufficient decongestion at discharge, or more comprehensive multidisciplinary transitional care management. In fact, we previously showed a nonlinear relationship between length of hospital stay and readmission; relatively short and long length of hospital stay were associated with increased rate of early HF readmission.[34] To further evaluate and establish these hypotheses precisely, a comprehensive assessment of congestion as well as the details of multidisciplinary intervention at discharge will likely be required.

Study Limitations

The present study has some limitations that should be considered when interpreting the results. First, this study was based on data from an observational registry and, despite covariate adjustment, unmeasured or unknown variables may have influenced the outcomes.

Table 3. Cox Proportional Hazard Analysis for Predicting All-Cause Death in the Overall Cohort

	HR	95% CI	*P* Value
Age	1.04	1.03–1.05	<0.001
Men	1.24	1.04–1.48	0.018
Previous HF admission	1.08	0.90–1.28	0.417
SBP	0.99	0.99–0.99	<0.001
Estimated glomerular filtration rate	0.99	0.99–1.00	<0.001
Sodium	0.95	0.93–0.97	<0.001
Hemoglobin	0.82	0.78–0.86	<0.001
LVEF	0.99	0.98–0.99	<0.001
β-Blockers	0.82	0.68–0.99	0.039
RAS inhibitors	0.68	0.57–0.80	<0.001
Mineralocorticoid receptor antagonists	1.07	0.89–1.29	0.455
90-d readmission	2.36	1.92–2.91	<0.001

HF indicates heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system; and SBP, systolic blood pressure.

Second, our findings might not be applicable to other countries, as discussed above. Third, it may be difficult to interpret the patients' New York Heart Association functional class at discharge, because they were patients with acute HF after in-hospital treatment, even with a long hospital stay and sufficient decongestion. Further investigations are warranted to elucidate whether New York Heart Association functional class at discharge in Japanese patients would be comparable to those at first visit after discharge in Western patients. Fourth, our study revealed that a significantly reduced use of loop diuretics was detected in patients admitted at 0 to 30 days compared with those admitted at 31 to 90 days, but the underlying mechanism still remains elusive. One of the plausible explanations for this is that the reduced use of loop diuretics could be associated with insufficient decongestion at discharge, which may consequently lead to a higher 30-day readmission rate. Comprehensive predischarge evaluation on congestion will be needed to examine this hypothesis. Finally, our registry did not obtain data on the number of readmissions in identical patients; the prognostic impact of the number of readmissions for a particular period (eg, 6 months) could not be evaluated; however, this has been described elsewhere.[35] Despite these limitations, this study highlights the continuous HF readmission beyond 30 days and its poor prognosis, which underlines the universal characteristics of patients readmitted with HF and challenges the current excessive focus on 30-day readmission bringing unintended consequence.

Table 4. Cox Proportional Hazard Analysis for Predicting All-Cause Death in 90-Day Readmitted Patients

	HR	95% CI	*P* Value
Age	1.03	1.01–1.05	0.013
Men	0.85	0.58–1.25	0.411
Previous HF admission	1.21	0.83–1.78	0.323
SBP	0.99	0.98–1.00	0.043
Estimated glomerular filtration rate	0.99	0.98–1.00	0.004
Sodium	0.95	0.90–0.99	0.027
Hemoglobin	0.93	0.84–1.02	0.128
LVEF	0.98	0.97–0.99	0.004
β-Blockers	0.43	0.29–0.64	<0.001
RAS inhibitors	0.62	0.42–0.90	0.012
Mineralocorticoid receptor antagonists	1.10	0.71–1.68	0.678

HF indicates heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system; and SBP, systolic blood pressure.

CONCLUSIONS

Among 90-day readmitted HF patients, approximately 60% of readmissions occurred beyond 30 days after discharge in a contemporary Japanese HHF registry. The readmitted patients within 90 days had higher risk of long-term mortality, regardless of the temporal proximity of readmission to the index hospitalization.

ARTICLE INFORMATION

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Disclosures

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Supplementary Materials

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Frequency of missing data.

	n	%
Variables		
Demographics and medical history		
Age	0	0.00
Male	0	0.00
BMI	166	4.62
Hypertension	1	0.03
Diabetes mellitus	3	0.08
Dyslipidemia	28	0.78
Atrial fibrillation	2	0.06
COPD	18	0.50
CKD	0	0.00
Stroke	13	0.36
Etiology of HF	0	0.00
Previous HF admission	30	0.84
NYHA at discharge	26	0.72
Vital signs at discharge		
Heart rate	24	0.67
SBP	19	0.53
Echocardiographic parameters		
LVEF	34	0.95
Laboratory data at discharge		
Hemoglobin	15	0.42
Sodium	18	0.50
eGFR	25	0.70
Lymphocyte	384	10.69
Total-Cholesterol	462	12.86

Medication or device therapy		
Loop diuretics	4	0.11
Beta-blockers	3	0.08
RAS inhibitors	2	0.06
MRA	142	3.95
ICD	3	0.08
CRT	4	0.11
Length of stay	0	0.00
SHFM Score	747	20.80
Prognostic information		
In-hospital death	0	0.00
HF-related readmission	0	0.00
Mortality	0	0.00

BMI: body mass index, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, HF: heart failure, NYHA: New York heart association, SBP: systolic blood pressure, LVEF: left ventricular ejection fraction, eGFR: estimated glomerular filtration rate, RAS: renin-angiotensin system, MRA: mineralocorticoid receptor antagonists, ICD: implantable cardioverter defibrillator, CRT: cardiac resynchronization therapy, SHFM: Seattle heart failure model.

Table S2. Cox proportional hazard analysis and Fine and Gray competing analysis for predicting 90-day readmission in overall cohort.

	Cox proportional hazard analysis	Competing risk analysis
	HR (95% CI, p-value)	HR (95% CI, p-value)
Age	1.02 (1.01-1.03, <0.001)	1.02 (1.01-1.03, 0.002)
Male	0.86 (0.70-1.06, 0.153)	0.83 (0.70-1.02, 0.074)
Previous HF admission	1.73 (1.40-2.13, <0.001)	1.82 (1.48-2.25, <0.001)
SBP	0.99 (0.98-1.00, 0.002)	0.99 (0.99-1.00, 0.016)
eGFR	1.00 (0.99-1.00, 0.161)	1.00 (0.99-1.00, 0.380)
Sodium	0.99 (0.96-1.01, 0.330)	1.00 (0.97-1.03, 0.800)
Hemoglobin	0.88 (0.83-0.93, <0.001)	0.90 (0.85-0.96, <0.001)
LVEF	0.99 (0.98-0.99, <0.001)	0.99 (0.98-1.00, 0.002)
Beta-blockers	0.98 (0.77-1.26, 0.881)	1.04 (0.81-1.33, 0.760)
RAS inhibitors	0.68 (0.56-0.84, <0.001)	0.75 (0.61-0.92, 0.005)
MRA	0.88 (0.71-1.10, 0.266)	0.91 (0.74-1.12, 0.370)

HR: hazard ratio, CI: confidence interval, HF: heart failure, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, RAS: renin-angiotensin system, MRA: mineralocorticoid receptor antagonists

Table S3. Cox proportional hazard analysis for predicting 30-day readmission in overall cohort.

	HR	95% CI	p Value
Age	1.02	1.00 - 1.03	0.016
Male	0.76	0.55 - 1.05	0.090
Previous HF admission	1.98	1.44 - 2.73	<0.001
SBP	1.00	0.99 - 1.01	0.846
eGFR	1.00	0.99 - 1.01	0.562
Sodium	0.99	0.94 - 1.03	0.466
Hemoglobin	0.94	0.86 - 1.03	0.160
LVEF	0.98	0.97 - 0.99	0.003
Beta-blockers	0.97	0.66 - 1.41	0.858
RAS inhibitors	0.53	0.39 - 0.72	<0.001
MRA	0.69	0.49 - 0.98	0.040

HR: hazard ratio, CI: confidence interval, HF: heart failure, SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, RAS: renin-angiotensin system, MRA: mineralocorticoid receptor antagonists.

Figure S1. Kaplan-Meier analysis demonstrating survival rate of readmitted patients and non-readmitted patients in 2-year-follow up with Landmark analysis at 0 day and 120 (A), 180 (B), and 360 (C) day.