



Association of Previous Hospitalization for Heart Failure With Increased Mortality in Patients Hospitalized for Acute Decompensated Heart Failure

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Background: We sought to explore the effects of previous heart failure (HF) hospitalization on mortality in patients hospitalized for acute decompensated HF (ADHF) in a large Japanese contemporary observational database.

Methods and Results: We prospectively enrolled consecutive patients with ADHF in 19 participating hospitals between October 2014 and March 2016. Of 4,056 patients, 1,442 patients (35.4%) had at least 1 previous HF hospitalization (previous hospitalization group), while 2,614 patients (64.5%) did not have a history of HF hospitalization (de novo hospitalization group). Patients with previous hospitalization were older and more often had comorbidities such as anemia, and renal failure than those without. The cumulative 1-year incidence of all-cause death was significantly higher in the previous hospitalization group than in the de novo hospitalization group (28% vs. 19%, $P < 0.001$). After adjusting confounders, the excess risk of the previous hospitalization group relative to the de novo hospitalization group for all-cause death remained significant (HR, 1.28; 95% CI: 1.10–1.50, $P = 0.001$). The excess risk was significant in patients without advanced age, anemia, or renal failure, but not significant in patients with these comorbidities, with significant interaction. Increase in the number of hospitalizations was associated with an increased risk for mortality.

Conclusions: In a contemporary ADHF cohort in Japan, repeated hospitalization was associated with an increasing, higher risk for 1-year mortality.

Key Words: Heart failure; Hospitalization; Mortality

Acute decompensated heart failure (ADHF) might be recognized as a “multi-event disease” with a high morbidity, mortality, and social burden.^{1,2} The natural history of heart failure (HF) included multiple occurrences of decompensated failure both symptomatically and hemodynamically, finally leading to death.³ Observational studies or subanalyses in randomized trial settings

from the late 1990s to the early 2000s illustrated the impact of previous hospitalization on long-term mortality in patients hospitalized for HF in Western countries.^{4–6} Rapid relief of symptoms, however, could be achieved once volume overload and/or excessive afterload were managed successfully in the acute decompensated phase. In addition, the recent advances in the management of HF and optimal

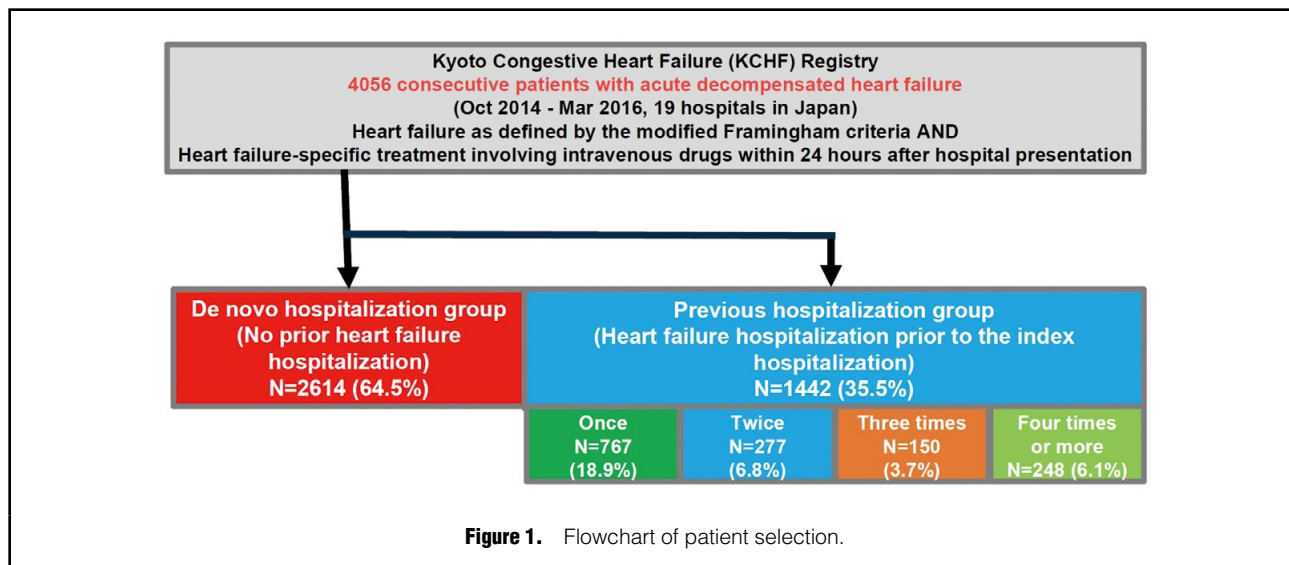
Received June 20, 2019; revised manuscript received September 24, 2019; accepted September 25, 2019; J-STAGE Advance Publication released online October 26, 2019 Time for primary review: 1 day

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guideline-recommended therapies often led clinicians to misunderstand that the patients have returned to their compensated state and some of these patients would tolerate repeated admissions; these patients were called “frequent flyers”.⁷ The aim of the current study was to explore the effects of previous HF hospitalization on mortality in patients hospitalized for ADHF in a large Japanese contemporary observational database.

Methods

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicenter cohort study that enrolled consecutive patients hospitalized due to ADHF for the first time between October 2014 and March 2016 in 19 secondary and tertiary hospitals, including rural and urban areas, and large and small hospitals, in Japan. The details of the design and patient enrolment in the KCHF registry have been described previously.^{8,9} Briefly, we enrolled patients with ADHF as defined by the modified Framingham criteria who were admitted to the participating centers, and those who underwent HF-specific treatment requiring i.v. drugs ≤ 24 h after presenting to hospital. We did not exclude those patients with ADHF associated with acute coronary syndrome (ACS). We collected not only the medical and laboratory data, but also the social and economic data. The study protocol was approved by the institutional review board of each participating center. Patient records were anonymized prior to analysis. A waiver of written informed consent from each patient was approved, because it was allowed in the Japanese ethics guidelines for epidemiological studies.¹⁰ Clinical follow-up data at 1 year were collected in October 2017. No patients refused to participate in the study when contacted for follow-up. The attending physicians or research assistants at each participating hospital collected the data for clinical events after the index hospitalization from the hospital charts, or by contacting patients, their relatives, and/or their referring physicians. In the present analysis, we sought to compare the clinical outcomes between patients with or without a previous history of HF hospitalization at the time of the index hospitalization for

ADHF (Figure 1).

Definitions

The primary outcome measure in the current analysis was all-cause death after the index admission for ADHF. We used the laboratory data at the time of the index admission. Renal failure was defined as estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² based on the chronic kidney disease grades. Anemia was defined using the World Health Organization criteria (hemoglobin < 12.0 g/dL in women and < 13.0 g/dL in men). Physical activity before admission was classified by mobility status based on the definition of Japanese long-term care insurance into ambulatory (including those patients using any aid such as a stick), use of wheelchair (outdoor only and indoor and outdoor), and bed-ridden state.^{8,9} Public financial assistance was defined as the public assistance system provided by the Japanese Government.¹¹ Patients with occupation were defined as those who were in a job or profession. Medical adherence was a dichotomous rating based on the self-report by patients or family members and reports by clinicians without rigorous quantitative definitions.^{12,13}

Statistical Analysis

Categorical variables are presented as n (%), and were compared using the chi-squared test. Continuous variables are expressed as mean \pm SD or median (IQR), and were compared using the Student's t-test when normally distributed or Wilcoxon rank-sum test when not normally distributed. Cumulative incidences were estimated using the Kaplan-Meier method and compared using the log-rank test. We regarded the date of admission as time zero for clinical follow-up. We compared baseline characteristics and mortality on the basis of the presence or absence of a previous HF hospitalization. We estimated the effects of previous HF hospitalization relative to no previous HF hospitalization for all-cause death as hazard ratios (HR) with 95% CI on multivariable Cox proportional hazard modeling. To adjust for the confounders, we simultaneously included previous HF hospitalization together with the 25 clinically relevant risk-adjusting variables in the multivariable Cox proportional hazards models in the entire cohort

and in the subgroups (Table 1), after proportional hazard assumptions were assessed on the plots of log (time) vs. log [−log (survival)] stratified by the variables and were verified to be acceptable. For the multivariable analyses, continuous variables were dichotomized using clinically meaningful reference values or medians: age >80 years based on the median; left ventricular ejection fraction (LVEF) <40%; body mass index (BMI) ≤22 kg/m²; eGFR <30 mL/min/1.73 m²; decreased albumin (serum albumin <3.0 g/dL); and hyponatremia (serum sodium <135 mEq/L) according to the previous study.¹⁴ Post-hoc subgroup analyses were conducted as stratified by age, LVEF, prior myocardial infarction (MI), anemia, and renal failure.

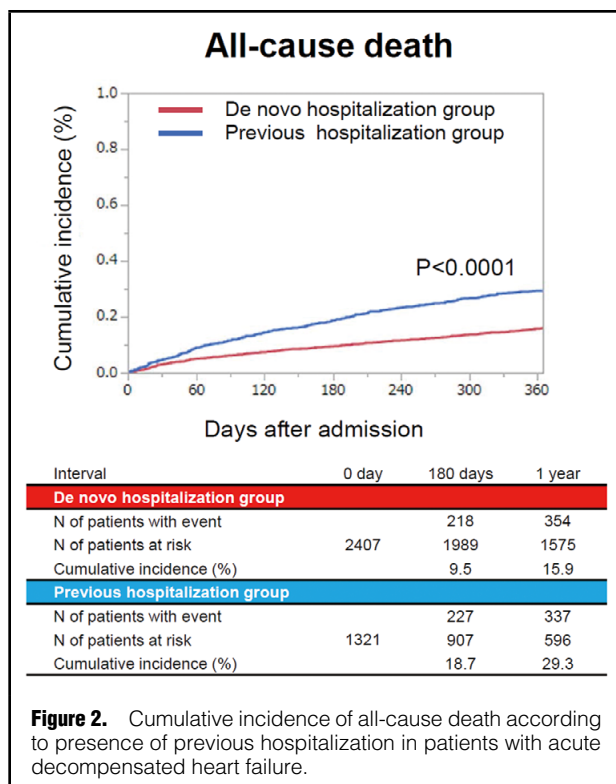
We further explored the effects of the number of previous HF hospitalizations on clinical outcome. Patients were divided into 5 groups on the basis of the number of previous HF hospitalizations: none, once, twice, three times, and four times or more, according to a previous study.⁵ Comparison of the 5 groups was performed using the chi-squared test for categorical variables and one-way analysis of variance in addition to the Cochran-Armitage trend test in order to assess the trend across the 5 groups. After proportional hazard assumptions for the 5 groups were assessed on the plots of log (time) vs. log [−log (survival)] stratified by the variables and were verified to be acceptable, we used a multivariable Cox proportional hazard model including

Table 1. ADHF Patient Characteristics			
Variables	Previous hospitalization group (n=1,442, 35.5%)	De novo hospitalization group (n=2,614, 64.5%)	P-value
Clinical characteristics			
Age (years)	81 (74–86)	80 (71–86)	0.001
Age >80 years [†]	821 (56.9)	1,326 (50.7)	<0.001
Men [†]	787 (54.6)	1,451 (55.5)	0.58
BMI (kg/m ²)	22.5 (20.0–25.2)	21.8 (19.6–24.8)	<0.001
BMI <22 kg/m ² [†]	718 (51.5)	1,069 (43.9)	<0.001
Etiology			
Cardiomyopathy	250 (17.3)	358 (13.7)	<0.001
Dilated cardiomyopathy	171 (11.9)	263 (10.1)	
Valvular heart disease	313 (21.7)	506 (19.3)	
Hypertensive	289 (20.0)	696 (26.6)	
Ischemic	492 (34.1)	835 (32.0)	
Associated with ACS [†]	33 (2.3)	206 (7.9)	
Not associated with ACS	459 (31.8)	629 (24.1)	
Arrhythmia-related	40 (2.7)	148 (5.7)	
Others	58 (4.0)	71 (4.0)	
Medical history			
AF or Afl [†]	756 (52.4)	925 (35.4)	<0.001
Hypertension [†]	1,009 (70.0)	1,900 (72.7)	0.07
DM [†]	599 (41.5)	911 (34.9)	<0.001
Dyslipidemia	625 (43.3)	924 (35.4)	<0.001
Prior MI [†]	441 (30.6)	467 (17.9)	<0.001
Prior stroke [†]	245 (17.0)	417 (16.0)	0.40
Prior PCI or CABG	535 (37.1)	485 (18.6)	<0.001
Current smoking [†]	130 (9.2)	346 (13.5)	<0.001
VT/VF	109 (7.6)	56 (2.1)	<0.001
Chronic lung disease [†]	214 (14.8)	322 (12.3)	0.03
Liver cirrhosis	16 (1.1)	39 (1.5)	0.40
Malignancy	220 (15.3)	365 (14.0)	0.26
Dementia	294 (20.4)	476 (18.2)	0.09
Social backgrounds			
Poor medical adherence	273 (18.9)	401 (15.3)	0.004
Living alone [†]	295 (20.5)	571 (21.8)	0.32
Employed	121 (8.4)	389 (14.9)	<0.001
Public financial assistance	103 (7.1)	131 (5.0)	0.006
Daily life activities			
Ambulatory [†]	1,068 (74.9)	2,081 (80.4)	<0.001
Use of wheelchair (outdoor only)	138 (9.7)	167 (6.5)	<0.001
Use of wheelchair (outdoor and indoor)	165 (11.6)	223 (8.6)	0.003
Bedridden	55 (3.9)	117 (4.5)	0.33

(Table 1 continued the next page.)

Variables	Previous hospitalization group (n=1,442, 35.5%)	De novo hospitalization group (n=2,614, 64.5%)	P-value
Vital signs at presentation			
SBP (mmHg)	142±34	150±36	<0.001
SBP <90mmHg [†]	55 (3.8)	71 (2.7)	0.06
Heart rate (beats/min)	92±25	98±29	<0.001
Heart rate <60beats/min [†]	72 (5.0)	193 (7.4)	0.003
NYHA class III or IV	1,267 (88.3)	2,270 (87.3)	0.37
Tests at admission			
LVEF (%)	45.0±16.7	46.6±16.0	0.005
LVEF <40% [†]	597 (41.5)	954 (36.7)	0.002
BNP (pg/mL)	757 (445–1,334)	696 (380–1,289)	0.008
Serum creatinine (mg/dL)	1.31 (0.97–1.92)	1.02 (0.79–1.47)	<0.001
eGFR <30mL/min/1.73m ² [†]	548 (38.1)	570 (21.9)	<0.001
BUN (mg/dL)	29 (20–43)	22 (17–32)	<0.001
Sodium <135 mEq/L [†]	198 (13.8)	321 (12.3)	0.20
Anemia ^{†,‡}	1,078 (74.8)	1,627 (62.4)	<0.001
Albumin <3.0g/dL [†]	188 (13.5)	379 (14.9)	0.24
Medication at admission			
ACEI or ARB [†]	750 (52.0)	1,100 (42.1)	<0.001
β-blocker [†]	840 (58.3)	720 (27.5)	<0.001
MRA [†]	434 (30.1)	299 (11.4)	<0.001
Loop diuretics [†]	1,123 (77.9)	853 (32.6)	<0.001
Tolvaptan [†]	139 (9.6)	31 (1.2)	<0.001
Length of hospital stay (days)	16 (11–26)	16 (11–24)	0.85

Data given as mean±SD, median (IQR) or n (%). [†]25 risk-adjusting variables selected for multivariable Cox proportional hazard modeling. [‡]Defined using the World Health Organization criteria (hemoglobin <12.0g/dL in women and <13.0g/dL in men). ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AF, atrial fibrillation; AFI, atrial flutter; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; VT/VF, ventricular tachycardia/fibrillation.



the number of prior HF hospitalizations as a continuous variable to estimate the impact on the primary outcome measure.

In additional analysis where we regarded the date of discharge as time zero for clinical follow-up, we further explored the effects of the number of previous HF hospitalizations on mortality in 3,728 patients discharged alive and with available follow-up data (**Supplementary Figure 1**). To adjust for the confounders, we included the aforementioned clinically relevant risk-adjusting variables and medication at discharge¹⁴ instead of medication at admission in the multivariable Cox proportional hazards models (**Supplementary Table 1**).

All statistical analyses were conducted by physicians (K.S. and T. Kato) and a statistician (T. Morimoto) using JMP 14.0 or SAS 9.4 (both SAS Institute, Cary, NC, USA). Two-tailed P<0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 4,065 study patients (median age, 80 years; IQR, 72–86 years; men, 55%; ischemic etiology, 33%; LVEF <40%, 38%), 1,442 patients (35.4%) had at least 1 previous HF hospitalization (previous hospitalization group), while 2,614 patients (64.5%) did not have a history of HF hospitalization (de novo hospitalization group; **Figure 1**). Patients in the previous hospitalization group were older, and more

Table 2. Primary and Secondary Outcomes in ADHF Patients

	Previous hospitalization group	De novo hospitalization group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
	No. patients with event/no. patients at risk (cumulative 1-year incidence, %)					
All-cause death	495/1,442 (27.9)	628/2,614 (18.5)	1.52 (1.35–1.71)	<0.001	1.28 (1.10–1.50)	0.001

ADHF, acute decompensated heart failure; CI, confidence interval; HR, hazard ratio.

Table 3. Subgroup Analysis for All-Cause Death in ADHF Patients

	Previous hospitalization group	De novo hospitalization group	Unadjusted		Adjusted		P-value for interaction
	No. patients with event/no. patients at risk (cumulative 1-year incidence, %)	No. patients with event/no. patients at risk (cumulative 1-year incidence, %)	HR (95% CI)	P-value	HR (95% CI)	P-value	
Age							
>80 years	342/821 (33.9)	458/1,326 (26.3)	1.27 (1.11–1.47)	<0.001	1.14 (0.94–1.37)	0.16	0.005
≤80 years	153/621 (20.0)	170/1,288 (10.7)	1.95 (1.57–2.43)	<0.001	1.73 (1.29–2.31)	<0.001	
LVEF							
LVEF <40%	212/597 (31.8)	228/954 (19.6)	1.58 (1.31–1.91)	<0.001	1.98 (1.58–2.47)	<0.001	0.49
LVEF ≥40%	280/841 (25.3)	395/1,649 (17.8)	1.46 (1.25–1.70)	<0.001	1.41 (1.08–1.86)	<0.001	
AF							
With AF	264/756 (27.2)	210/925 (18.8)	1.64 (1.37–1.98)	<0.001	1.18 (0.94–1.48)	0.15	0.93
Without AF	231/686 (28.5)	418/1,689 (18.1)	1.43 (1.22–1.68)	<0.001	1.14 (0.93–1.41)	0.21	
DM							
With DM	180/599 (24.9)	208/911 (17.9)	1.37 (1.12–1.68)	0.002	1.00 (0.77–1.30)	0.99	0.38
Without DM	315/843 (30.0)	420/1,703 (18.9)	1.63 (1.41–1.89)	<0.001	1.32 (1.10–1.60)	0.004	
Prior MI							
With prior MI	149/441 (28.2)	127/467 (21.3)	1.26 (1.00–1.60)	0.05	1.00 (0.74–1.35)	0.999	0.13
Without prior MI	346/1,001 (27.8)	501/2,147 (17.9)	1.59 (1.38–1.82)	<0.001	1.25 (1.05–1.49)	0.014	
Anemia							
With anemia	399/1,078 (29.8)	492/1,627 (23.1)	1.26 (1.10–1.43)	<0.001	1.10 (0.93–1.30)	0.29	0.003
Without anemia	95/363 (22.1)	136/981 (11.2)	2.05 (1.58–2.66)	<0.001	1.65 (1.16–2.35)	0.006	
Renal failure							
eGFR <30 mL/min/1.73 m ²	234/548 (35.0)	212/570 (29.7)	1.17 (0.97–1.41)	0.10	1.03 (0.81–1.32)	0.80	0.04
eGFR ≥30 mL/min/1.73 m ²	260/892 (23.5)	414/2,039 (15.4)	1.51 (1.29–1.76)	<0.001	1.26 (1.03–1.53)	0.02	

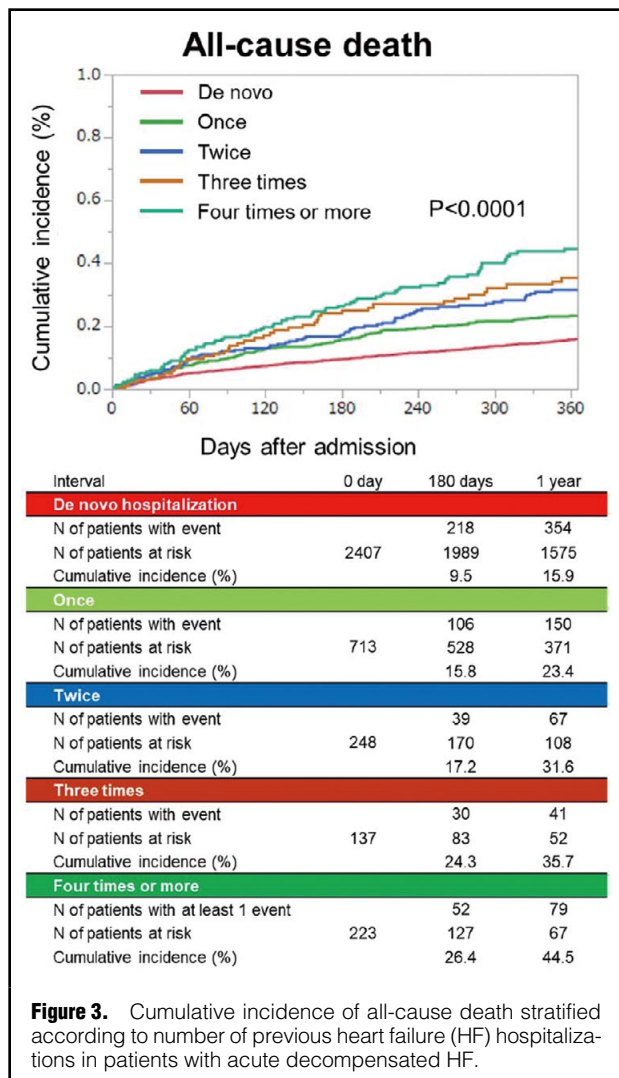
Abbreviations as in Tables 1,2.

often had a smaller BMI, diabetes mellitus, prior MI, atrial fibrillation or flutter, and ventricular arrhythmias than those in the de novo hospitalization group (Table 1). Patients in the prior hospitalization group less often had hypertension and ACS as the underlying heart disease, and less often were current smokers, and ambulatory. Regarding social background, patients with previous hospitalization more often had poor medical adherence and received public financial assistance, and less often were employed. Patients

with prior hospitalization had lower systolic blood pressure, and lower LVEF, and more often had renal dysfunction, anemia, and higher brain natriuretic peptide than those without prior hospitalization (Table 1).

Clinical Outcomes

Follow-up rate at 1 year was 94%. The cumulative 1-year incidence of all-cause death was significantly higher in the previous hospitalization group than in the de novo hospi-



talization group (28% vs. 19%, $P < 0.001$; **Figure 2**). After adjusting for confounders, the excess risk of the previous hospitalization group relative to the de novo hospitalization group for all-cause death remained significant (HR, 1.28; 95% CI: 1.10–1.50, $P = 0.001$; **Table 2**).

Subgroup Analysis

On subgroup analyses, the excess risk of the previous hospitalization group relative to the de novo hospitalization group for all-cause death was significant in patients ≤ 80 years of age, patients without anemia, and patients without renal failure, but not significant in patients > 80 years of age, patients with anemia, and patients with renal failure, with significant interaction. There was no interaction between the subgroup factors LVEF, diabetes, prior MI, and atrial fibrillation, and the effect of previous hospitalization relative to de novo hospitalization for all-cause death (**Table 3**).

Clinical Outcomes According to Number of Previous Hospitalizations

Patients were classified based on the number of previous hospitalizations: none, $n = 2,614$ (64.5%); once, $n = 767$ (18.9%); twice, $n = 277$ (6.8%); three times, $n = 150$

(3.7%); and four times or more, $n = 248$ (6.1%; **Supplementary Table 2**). Baseline characteristics in the 5 groups based on the number of previous hospitalizations are listed in **Supplementary Table 1**. The cumulative 1-year incidence of all-cause death was higher as the number of previous hospitalizations increased (**Figure 3**). The increasing number of hospitalizations was associated with an increasing higher risk for all-cause death (HR per 1-grade increase, 1.12; 95% CI: 1.05–1.19, $P < 0.001$).

Additional Analysis

When we analyzed 3,728 patients discharged alive, the trend was fully consistent with the main analysis (**Supplementary Figure 2; Supplementary Table 3**).

Discussion

The main findings of the present study are as follows: (1) previous history of HF hospitalization in patients hospitalized for ADHF was associated with a higher risk for mortality; (2) on subgroup analysis, the excess risk of previous hospitalization relative to de novo hospitalization for all-cause death was significant in patients ≤ 80 years of age, patients without anemia, and patients without renal failure, but not significant in patients > 80 years of age, patients with anemia, and patients with renal failure, with significant interaction; and (3) the cumulative 1-year incidence of all-cause death increased with increasing number of previous hospitalizations.

The mean age of patients hospitalized for ADHF is getting older, with a larger proportion of HF with preserved ejection fraction.^{9,15} The average age of patients enrolled in REALITY-AHF conducted in 2014–2015 was 78 years,¹⁶ and the median age of patients enrolled in the present study was 80 years. The proportion of previous hospitalizations for HF was 36% in the ATEND registry conducted in 2007–2011,¹⁷ and 30% for the WET-HF registry conducted in 2011–2015,¹⁸ which is similar to the 35% in the present study. From the WET-HF registry, Akita et al reported that a history of multiple previous HF admissions was an independent and strong risk factor for adverse events in ADHF patients discharged alive.¹⁹ The present result is in line with the previous studies.^{4–6,19} The present findings, however, are novel in Japan because we analyzed the association between the history of previous hospitalization and mortality, starting from presentation to hospital, in conjunction with social background, and found that an increasing number of prior hospitalizations was associated with an increasing, higher mortality during a relatively short follow-up duration of 1 year. Therefore, the prevention of ADHF, regardless of whether the episode is the first or second or more, would be critically important in the management of HF. The threshold for the decision on hospitalization can be influenced by severity of HF and comorbidity, as well as by differences in practice pattern between hospitals, physicians, or locality. We adjusted for the former by including those baseline covariates that affected death in the overall multivariable mortality model. The present data are in line with evidence in Canada and the USA,^{4,6} and can be generalized, although the previous studies analyzed chronic HF patients⁶ or patients discharged alive in ADHF;^{4,5} and none analyzed the entire clinical course starting from presentation to hospital.

In patients < 80 years of age and in those without anemia or without renal failure, prior history of HF hospitalization

was associated with a significantly higher 1-year mortality. This indicates that young patients without anemia or without renal failure need special attention to prevent HF deterioration before they develop symptoms and need hospitalization. Regarding the LVEF, several drugs for HF (e.g., angiotensin-converting enzyme inhibitors,^{20,21} β -blockers,^{22,23} and mineralocorticoid receptor antagonists²⁴) have been proven to reduce mortality in patients with HF with reduced LVEF, and have been widely applied in daily practice. Previous hospitalization was still associated with mortality regardless of LVEF after adjustment for these drugs. The trend was consistent with a previous Japanese study,¹⁹ except for the interaction when we stratified by age, renal dysfunction, and anemia. The discrepancy may be due to the difference in the endpoint of all-cause death alone or a composite endpoint of death and HF hospitalization, along with the number of patients with events or enrolled.

An increase in mortality with the increasing number of hospitalizations might indicate the importance of decreasing the number of hospitalizations even once. Some patients who tolerate repeated admissions are called “frequent flyers”, but they are progressing toward death.⁵ We assessed medical adherence, public financial support, living alone, cognitive dysfunction, and physical status. Consistently with previous studies,^{25–28} patients with prior HF hospitalization more often had poor medical adherence; further, they more often received social support and less often were employed compared with patients with de novo hospitalization. The present results might have significant implications for the clinical care for HF in Japan. The cause-effect relationship between these unfavorable social conditions and repeated hospitalizations was not determined in the present study, but patients with recurrent HF admissions would need to be carefully evaluated to determine whether they have poor health literacy, and should be educated on the prevention of HF exacerbation,^{25,27} and, in some cases, should be supported physically or financially by public resources to improve medical adherence,^{26,29} and ultimately to maintain the compensated state of HF.³⁰

Study Limitations

There were several notable limitations in the present study. The primary variable was the previous hospitalization, and therefore, milder forms of ADHF that are managed without hospitalization were not taken into consideration in the present study. In addition, we did not collect data on the interval from the previous hospitalization to the index hospitalization.

It is likely that additional factors beyond HF severity and clinical practice might have been related to the repeated hospitalizations, such as the lower threshold for hospitalization in patients with prior hospitalization. Nonetheless, repeated hospitalization was independently associated with all-cause death. Finally, there are unmeasured confounders that influence the effect of previous hospitalization on mortality.

Conclusions

In a contemporary ADHF cohort in Japan, repeated hospitalization was directly proportional to a higher risk for 1-year mortality.

Disclosures

This study is supported by a grant from the Japan Agency for Medical Research and Development (18059186) to T. Kato, K.K., N.O. The founder had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication. K.K. is a member of *Circulation Reports*' Editorial Team.

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circrep.CR-19-0054>