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Risk Factors and Clinical Outcomes of Functional Decline during Acute Decompensated Heart Failure Hospitalization: Observations from the KCHF Registry

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Abstract

Objective: To investigate the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in patients with acute decompensated heart failure (ADHF) hospitalization.

Design: Prospective cohort study between October 1, 2014, and March 31, 2016.

Setting: A physician-initiated multicentre study of consecutive patients admitted for ADHF into 1 of 19 secondary and tertiary hospitals throughout Japan.

Participants: Among 3555 patients hospitalized for ADHF (median age [IQR], 80 [71-86] years; 1572 [44%] women), functional decline during the index hospitalization occurred in 528 patients (15%).

Primary and secondary outcomes: The primary outcome measure was a composite of all-cause death or heart failure hospitalization after discharge. The secondary outcome measures were all-cause death and heart failure hospitalization.

Results: The independent risk factors for functional decline included age ≥80 years (OR 2.56; 95% CI 1.98–3.32), women (OR 1.27; 95% CI 1.01–1.60), prior stroke (OR 1.61; 95% CI 1.23–2.10), dementia (OR 1.95; 95% CI 1.52–2.52), elevated body temperature (OR 1.88; 95% CI 1.29–2.74), hyponatremia (OR 1.46; 95% CI 1.07–1.98), decreased albumin levels

(OR 1.69; 95% CI 1.27–2.24), renal dysfunction (OR 1.54; 95% CI 1.21–1.96), and New York Heart Association class III/IV on admission (OR 1.51; 95% CI 1.05–2.18) after multivariable adjustment. The cumulative 1-year incidence of the primary outcome in the functional decline group was significantly higher than that in the no functional decline group (50% vs. 31%, log-rank P<0.001). After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR 1.50; 95% CI 1.29–1.75; P<0.001).

Conclusions: Independent risk factors of functional decline in ADHF patients were related to both frailty and severity of heart failure. Functional decline during hospitalization was associated with unfavourable post-discharge outcomes.

Trial Registration: https://clinicaltrials.gov/ct2/show/NCT02334891 (NCT02334891) and https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000017241 (UMIN000015238)

Strengths and limitations of this study

- This study is the first large-scale contemporary multicentre study reporting the prevalence of functional decline in patients hospitalized for acute decompensated heart failure (ADHF).
- Functional decline during hospitalization occurred in 15% of patients, and 80% of those with functional decline were ambulatory before admission
- The severity of symptoms or patient status specific for heart failure was associated with functional decline independent of well-known factors in acute medical illness.
- Functional decline during ADHF hospitalization was statistically significantly associated with a higher risk for the primary composite outcome of mortality or heart failure readmission.
- We did not collect data regarding on-site and outpatient rehabilitation and nutritional support.

Introduction

Functional decline in hospitalized patients is a complex and dynamic process [1–3]. Functional decline during hospitalization was reported to occur in approximately 30-50% of patients hospitalized for acute medical illness [2,4,5]. In the rapidly aging societies, the number of patients hospitalized for acute decompensated heart failure (ADHF) is increasing, and ADHF has become the leading cause of hospitalization due to acute medical illness. In older patients, functional decline associated with hospitalization often leads to subsequent inability to live actively and independently.

However, there is a scarcity of data regarding the risk factors of functional decline in patients hospitalized for ADHF. Identifying high-risk patients for functional decline during hospitalization would be useful for its prevention. Furthermore, no previous study focused on subsequent clinical outcomes in patients with functional decline during hospitalization. Therefore, we sought to clarify the risk factors for functional decline during hospitalization in patients with ADHF and to compare the 1-year clinical outcomes between the 2 groups of patients with and without functional decline during the hospitalization for ADHF in a large Japanese observational database of hospitalized patients for ADHF in the real-world clinical practice.

Methods

Study Design, Setting, and Population

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled consecutive patients who were hospitalized for ADHF for the first time between October 1, 2014, and March 31, 2016. These patients were admitted into 19 secondary and tertiary hospitals, including rural and urban as well as large and small institutions, throughout Japan. The study protocol was approved by the institutional review board of each participating hospital. A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating centre because the study met the conditions of the Japanese ethical guidelines for epidemiological study and the US policy for protecting human research participants.[6,7] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The details of the KCHF study design and patient enrolment are described elsewhere.[8,9] Briefly, we enrolled all patients with ADHF, as defined by the modified Framingham criteria, who were admitted to the participating hospitals and patients who underwent heart failure–specific treatment involving intravenous drugs within 24 hours after

hospital presentation. Patient records were anonymized before analysis. Data analysis was conducted from August 2018 to October 2018.

Among 4056 patients enrolled in the KCHF registry, 3785 patients were discharged alive after hospitalization for ADHF. Clinical follow-up data were collected in October 2017. The attending physicians or research assistants at each participating hospital collected clinical events after the index hospitalization from hospital charts or by contacting patients, their relatives, or their referring physicians with consent. The present analysis had 2 objectives. First, we sought to clarify the risk factors for functional decline during hospitalization of ADHF patients. Second, we sought to compare the 1-year clinical outcomes between the 2 groups of patients with and without functional decline during the hospitalization for ADHF. Among 4056 patients enrolled in the KCHF registry, the current study population consisted of 3555 patients who were discharged alive and were assessed for functional decline during hospitalization, excluding 271 patients who died during the index hospitalization, 99 patients whose functional status before admission and/or at discharge was not available, and 131 patients who were bedridden before index hospitalization (Figure 1). The long-term follow-up was censored at 1-year. The primary outcome measure in the current analysis was a composite of all-cause death or heart failure hospitalization at 1-year. The secondary

outcome measures were all-cause death and heart failure hospitalization.

Definitions

Physical activity before admission and at discharge 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 stick), use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state [8]. Functional decline was defined as the decline of at least one stage on physical activity at discharge compared with pre-admission status. In-hospital worsening heart failure was defined as additional intravenous drug administration for heart failure, haemodialysis, or mechanical circulatory or respiratory support, occurring >24 hours after therapy initiation [10]. In-hospital worsening renal function was defined as >0.3 mg/dL increase in serum creatinine levels during the index hospitalization [11–13]. Detailed definitions of baseline clinical characteristics including the signs and symptoms of heart failure were described previously [9].

Statistical Analysis

Categorical variables were presented as numbers with percentages and compared using χ^2 test. Continuous variables were expressed as the mean with standard deviation or median with 25th to 75th percentiles, and compared using the Student's *t* test when normally

distributed or Wilcoxon rank-sum test when not normally distributed.

We compared baseline characteristics and clinical outcomes based on the presence or absence of functional decline during the index hospitalization. A multivariable logistic regression model was developed to identify clinical characteristics associated with an increased risk for functional decline. We used 23 clinically relevant factors listed in Table 1 as potential independent risk factors in the multivariable logistic regression model and estimated the odd ratios (ORs) and 95% confidence intervals (CIs). We used the Kaplan-Meier method to estimate the cumulative 1-year incidences of the outcome measures and assessed the differences with the log-rank test. We expressed the associations of the functional decline group with the no functional decline group for all outcome measures as hazard ratios (HRs) with 95% CIs by multivariable Cox proportional hazard models incorporating the 23 clinically relevant risk-adjusting variables indicated in Table 1. We also conducted subgroup analyses stratified by age, sex, LVEF, anaemia, albumin levels, body temperature, and the symptomatic status at discharge (oedema and general malaise at discharge). In the multivariable analysis and subgroup analyses, continuous variables were dichotomized by clinically meaningful reference values or median values; age ≥80 years based on the median value, LVEF <40% based on the heart failure guideline of LVEF

classification [14], BMI ≤22 kg/m^2, renal dysfunction (eGFR <30 ml/min/1.73m^2) based on CKD grade, decreased albumin levels (serum albumin <3.0 g/dL), hyponatremia (serum sodium <135 mEq/L), elevated body temperature (body temperature ≥37.5℃) based on the cut-off value in metabolic syndrome [15].

We performed an additional analysis using the data including those patients who died during the index hospitalization and those who were bedridden before the index hospitalization, and evaluated the factors associated with functional decline or in-hospital mortality by constructing multivariable adjusted Cox models. All statistical analyses were conducted by a physician (H.Y.) and a statistician (T.M.) with JMP 13.0 or SAS 9.4 (both SAS Institute Inc, Cary, NC). Two-tailed P-values less than 0.05 were considered statistically significant.

Patient and public involvement

No patient involved.

Results

Baseline Clinical Characteristics

Among 3555 study patients, physical activity before admission included

ambulatory in 2949 patients (83%), wheelchair outdoor only in 272 patients (7.7%), and wheelchair outdoor and indoor in 334 patients (9.4%). At hospital discharge, functional decline was observed in 420 patients (14%) who were ambulatory before admission, in 80 patients (29%) who had used wheelchair outdoor only, and in 28 patients (8.4%) who had used wheelchair outdoor and indoor. Consequently, decline in functional status was observed in 528 patients (15%; functional decline group), while functional decline was not observed in 3027 patients (85%; no functional decline group) (eFigure 1). Wheelchair outdoor only before admission were more prevalent in the functional decline group than in the no functional decline group; however, 80% of patients in the functional decline group were ambulatory before admission (Table 1).

Regarding the baseline clinical characteristics, the patients in the functional decline group were older and had a higher prevalence of hypertension, prior stroke, renal dysfunction, dementia, malignancy, anaemia, decreased albumin levels, and hyponatremia (Table 1). There were no significant differences in previous heart failure hospitalization, atrial fibrillation or flutter, previous myocardial infarction, chronic lung disease, and living alone status as a social background between the 2 groups (Table 1). The functional decline group was more likely to have a valvular aetiology, lower blood pressure, lower heart rate,

higher levels of brain natriuretic peptide (BNP) or N-terminal portion of proBNP (NT-proBNP), and a higher LVEF (Table 1). The proportion of patients who achieved relief of signs and symptoms on admission after the treatment in the emergency room was not significantly different between the 2 groups (14% vs. 16%, P=0.25).

Risk Factors for Functional Decline

Among the baseline characteristics and status at hospital presentation, the following independent risk factors for functional decline during hospitalization were identified by the multivariable logistic regression analysis: age ≥80 years (OR 2.56; 95% CI 1.98–3.32), women (OR 1.27; 95% CI 1.01–1.60), prior stroke (OR 1.61; 95% CI 1.23–2.10), dementia (OR 1.95; 95% CI 1.52–2.52), body temperature ≥37.5℃ (OR 1.88; 95% CI 1.29–2.74), hyponatremia (OR 1.46; 95% CI 1.07–1.98), decreased albumin levels (OR 1.69; 95% CI 1.27–2.24), eGFR <30 ml/min/1.73m^2 (OR 1.54; 95% CI 1.21–1.96), and New York Heart Association (NYHA) class III/IV on admission (OR 1.51; 95% CI 1.05–2.18) (Figure 2 and eTable 1).

In-hospital adverse events and status at discharge

The median length of hospital stay was longer in the functional decline group than in the no functional decline group (21 days vs. 15 days, P <0.001). Regarding the in-hospital

adverse events, the prevalence of worsening heart failure, worsening renal function, and stroke was higher in the functional decline group than in the no functional decline group (Table 2). The proportion of patients with symptoms such as dyspnoea on exertion, oedema, general malaise, and loss of appetite at discharge was higher in the functional decline group than in the no functional decline group (Table 2). Consequently, the proportion of patients in the functional decline group discharged to home was also lower (47% vs. 90%, P <0.001). Regarding medical treatment at discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB), and beta blocker were less often prescribed in the functional decline group than in the no functional decline group (Table 2).

Long-term outcomes: functional decline vs. no functional decline groups

Follow-up rate at 1-year was 96%. The cumulative 1-year incidence of the primary outcome measure (a composite of all-cause death or heart failure hospitalization) in the functional decline group was significantly higher than that in the no functional decline group (50% vs. 31%, log-rank P<0.001) (Figure 3). After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR, 1.50; 95%CI, 1.29–1.75; P<0.001) (Figure 3 and eTable 2). The cumulative 1-year incidence of all-cause death was also significantly higher in the

functional decline group than in the no functional decline group. Even after adjusting confounders, the excess mortality risk of the functional decline group relative to the no functional decline group remained significant (Figure 3 and eTable 2). The cumulative 1-year incidence of heart failure hospitalization was also significantly higher in the functional decline group than in the no functional decline group. However, the adjusted risk of the functional decline group relative to the no functional decline group for heart failure hospitalization was no longer significant (Figure 3 and eTable 2). In the subgroup analyses, there were no interactions between those subgroup factors and the association of functional decline with the primary outcome measure (eFigure 2).

Additional analysis on the risk factors for functional decline or in-hospital mortality

The risk factors for functional decline or in-hospital mortality in a total of 4056 patients were similar to the risk factors for functional decline. LVEF <40% (OR, 1.23; 95% CI, 1.00–1.52) and acute coronary syndrome (OR, 1.73; 95% CI, 1.17–2.56) that were not included in the risk factors for functional decline emerged as the risk factors for functional decline or in-hospital mortality. Meanwhile, among the risk factors for functional decline, women (OR, 1.10; 95% CI, 0.90–1.34) was not included in the risk factors for functional decline or in-hospital mortality (Figure 2 and eTable 1).

Discussion

The main findings of the present study investigating the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in patients with ADHF hospitalization were as follows; 1) Functional decline during hospitalization occurred in 15% of patients, and 80% of those with functional decline were ambulatory before admission; 2) The independent baseline risk factors associated with functional decline included age ≥80 years, women, prior stroke, dementia, body temperature ≥37.5ºC, hyponatremia, decreased albumin levels, eGFR <30 ml/min/1.73m^2, and NYHA class III/IV; 3) Functional decline during the index hospitalization was associated with higher long-term risk for a composite of all-cause death or heart failure hospitalization.

This is the first large-scale contemporary multicentre study reporting the prevalence of functional decline in patients hospitalized for ADHF. Of note, we identified the severity of symptoms or patient status specific for heart failure was associated with functional decline independent of well-known factors in acute medical illness [16–18]. Functional decline is an inevitable consequence in aged people, but hospitalization accelerates the decline [18–20]. Functional declines have been found to be related not only to impairment of

independence and quality of life (QOL), but also to increased health service use, higher risk for institutionalization, and higher risk for mortality [21–25]. Indeed, in the present study, the proportion of patients discharged to home was lower in the functional decline group than in the no functional decline group, suggesting impaired QOL after discharge. Also, the long-term mortality was worse in the functional decline group than in the no functional decline group. Therefore, it is important to recognize risk factors of functional decline. In previous studies of hospitalized patients with acute medical illness, the predictors of functional decline in hospitalized elderly patients were older age, admission diagnosis, lower functional status, impaired cognitive status, comorbidities, and length of hospital stay [16–18]. These findings were confirmed in the setting of ADHF in our present study. In addition, findings specific for ADHF such as the dyspnoea or hyponatremia was associated with functional decline, which were also reported to be the risk factors for in-hospital mortality in ADHF [26]. The prevalence of dyspnoea, oedema, general malaise and loss of appetite at discharge was higher in the functional decline group. Early achievement of successful ADHF treatment might reduce the risk of functional decline, although the present observational study could not address the cause-effect relationship between the functional decline and the symptomatic status at discharge.

There might be several possible strategies to prevent functional decline during ADHF hospitalization. The first is the early improvement of hemodynamic status to avoid worsening heart failure. The prevalence of worsening heart failure was higher in the functional decline group. As functional decline associated with hospitalization begins within 48 hours of admission, early improvement of heart failure to reduce the incidence of hospitalization-associated disability is one of the main goals of care [26]. Second, it would be important to be adequately aware high-risk patients to make aggressive intervention for preventing functional decline. We identified the risk factors among the baseline characteristics in ADHF patients. In addition, the adverse events during hospitalization may be tightly related to the functional decline. Stroke is one of causes of functional decline and observed in 5.1% of patients with functional decline. Third, a strategy for the prevention of functional decline might be the seamless rehabilitation and comprehensive geriatric management through a multidisciplinary team approach [27–30]. In addition, the subgroup analysis showed that there were no interactions between those subgroup factors and the association of functional decline with the primary outcome measure. Thus, prevention of functional decline would have an impact on improving outcomes in all of the patients with ADHF.

This study has several limitations. First, we did not collect information on activity of daily living index. Instead, we adopted easy and simple classification of functional status as ambulatory, use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state. Second, we did not collect data regarding on-site and outpatient rehabilitation and nutritional support. However, a team-based approach for heart failure patients was adapted in all the participating centres in the present study. Third, we did not include the status at discharge or adverse in-hospital events in the analysis for the risk factor for functional decline, because the cause-effect relationship was not clear. Fourth, data on post-discharge medication and change of functional status after discharge from the index hospitalization were not collected, and not analysed in the analysis for the long-term outcomes. Fifth, as with any observational study, the possibility of selection bias and residual confounding cannot be excluded, although we adjusted for 23 variables as most conceivable confounders.

Conclusions

Independent risk factors of functional decline in ADHF patients were related to both frailty and severity of heart failure. Functional decline during ADHF hospitalization was associated with unfavourable post-discharge outcomes.

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H.Yaku and T.Kato had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

None

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Figure legends

Figure 1. **Patient Flowchart.** KCHF=Kyoto Congestive Heart Failure, ADHF=acute decompensated heart failure.

Figure 2. Clinical Factors Associated with Functional Decline during Hospitalization in the Univariate and Multivariable Logistic Regression Models. BMI=body mass index, LVEF=left ventricular ejection, HF=heart failure, eGFR=estimated glomerular filtration rate, BP=blood pressure, NYHA=New York Heart Association, OR=odds ratio, CI=confidence interval.

Figure 3. **The Cumulative Incidences for the Primary Outcome Measure (A), for All-cause Death (B), and for HF Hospitalization (C) According to the Presence or Absence of Functional Decline.** HF=heart failure, HR=hazard ratio, CI=confidence interval.

Table 1. Baseline Patient Characteristics

	Functional decline	No functional decline	P value
	N=528	N=3027	
Baseline characteristics			
Age, years	85 [80–89]	79 [70–85]	<0.001
Age ≥80 years*	399 (76)	1407 (46)	<0.001
Women*	294 (56)	1278 (42)	<0.001
BMI, kg/m^2	22.0±4.0	23.1±4.5	<0.001
BMI ≤22 kg/m^2*	269 (55)	1281 (44)	<0.001
Medical history			
Prior HF hospitalization*	186 (36)	1077 (36)	0.92
Atrial fibrillation/flutter*	220 (42)	1263 (42)	0.98
Hypertension*	406 (77)	2174 (72)	0.02
Diabetes mellitus*	187 (35)	1145 (38)	0.29
Prior myocardial infarction*	112 (21)	681 (23)	0.51
Prior stroke*	125 (24)	432 (14)	<0.001
Current smoking*	28 (5.5)	425 (14)	<0.001
Malignancy	97 (18)	419 (14)	0.006
Chronic lung disease*	41 (7.8)	247 (8.2)	0.76
Dementia*	175 (33)	423 (14)	<0.001
Social backgrounds			
Poor medical adherence	100 (19)	498 (16)	0.16
Living alone*	127 (24)	652 (22)	0.20
Public assistance	24 (4.6)	186 (6.1)	0.14
Functional status before admission			
Ambulatory	420 (80)	2529 (84)	0.02
Use of wheelchair [outdoor only]	80 (15)	192 (6.3)	<0.001
Use of wheelchair [outdoor and indoor]	28 (5.3)	306 (10)	<.0001
Underlying heart disease			
Ischemic	134 (25)	820 (27)	0.41

Acute coronary syndrome*	36 (6.8)	166 (5.5)	0.22
Hypertensive	131 (25)	754 (25)	0.96
Valvular	124 (23)	565 (19)	<0.001
Cardiomyopathy	54 (10)	492 (16)	<0.001
Clinical signs and symptoms at presentation			
Orthopnoea (moderate or severe)	321 (64)	1743 (60)	0.09
Rales (moderate or severe)	302 (59)	1522 (52)	0.002
Systolic BP, mmHg	144±32	149±35	0.003
Systolic BP ≥140 mmHg	275 (53)	1741 (58)	0.03
Systolic BP <90 mmHg*	12 (2.3)	76 (2.5)	0.76
Diastolic BP, mmHg	81±23	86±24	<0.001
Heart rate, beat/min	93±27	96±28	0.001
Heart rate <60 beat/min*	44 (8.5)	195 (6.5)	0.11
Body temperature, ºC	36.6±0.7	36.5±0.6	<0.001
Body temperature ≥37.5ºC*	58 (11)	154 (5.3)	<0.001
Data on admission			
Orthopnoea (moderate or severe)	208 (44)	1090 (40)	0.08
Rales (moderate or severe)	213 (47)	1021 (39)	0.001
Systolic BP, mmHg			
Systolic BP ≥140 mmHg	198 (38)	1199 (40)	0.29
Systolic BP <90 mmHg	8 (66)	58 (2.0)	0.51
Heart rate, beat/min	86±21	89±23	0.03
Echocardiography and Laboratory tests			
LVEF	48±16	46±16	0.02
HFrEF (EF<40%)*	167 (32)	1148 (38)	0.006
HFmrEF (EF 40–49%)	117 (22)	566 (19)	0.06
HFpEF (EF ≥50%)	242 (46)	1305 (43)	0.24
Haemoglobin, g/dL	11.0±2.1	11.7±2.4	<0.001
Anaemia*†	401 (76)	1946 (64)	<0.001
BNP, pg/ml	782 [448–1410]	687 [375–1214]	<0.001
NT-pro BNP, pg/ml	10795 [3450–18000]	5416 [2629–11438]	0.001
Creatinine, mg/dL	1.2 [0.8–1.6]	1.1 [0.8–1.6]	0.21
eGFR, ml/min/1.73m^2	38 [24–54]	46 [30–62]	<0.001

eGFR <30 ml/min/1.73m^2*	195 (37)	747 (25)	<0.001
Blood urea nitrogen, mg/dL	28 (20–39)	23 (17–33)	<0.001
Albumin, g/dL	3.3±0.5	3.5±0.5	<0.001
Albumin <3.0 g/dL*	112 (22)	332 (11)	<0.001
Sodium, mEq/L	138±4.7	139±4.1	<0.001
Sodium <135 mEq/L*	83 (16)	325 (11)	0.001
Potassium, mEq/L	4.3±0.8	4.2±0.6	0.03

Continuous variables were presented as mean ± SD or median with [interquartile range]. Categorical variables were presented as number (percentage).

* Risk-adjusting variables selected for Cox proportional hazard models.

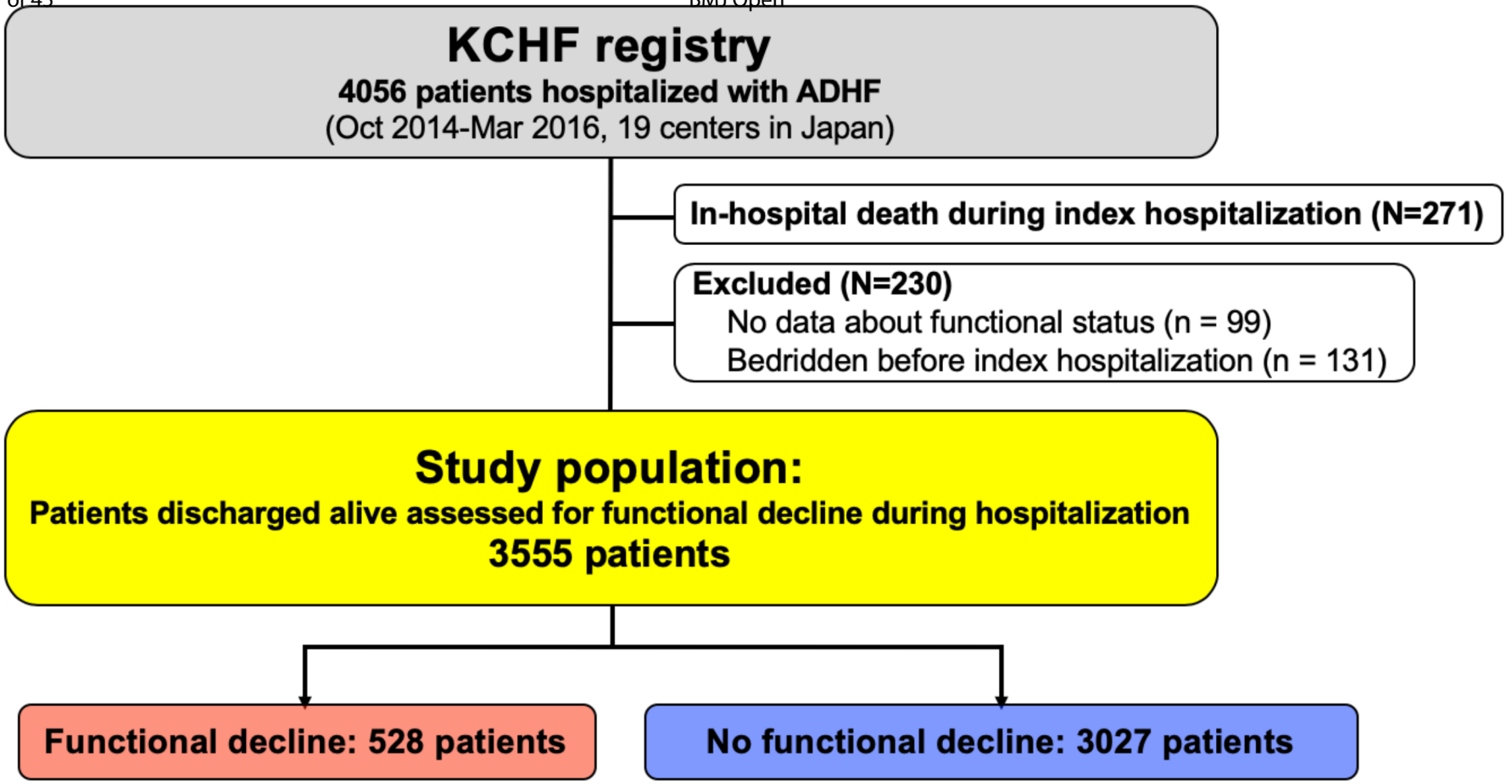
† Defined by the World Health Organization criteria (haemoglobin <12 g/dL for women and <13 g/dL for men).

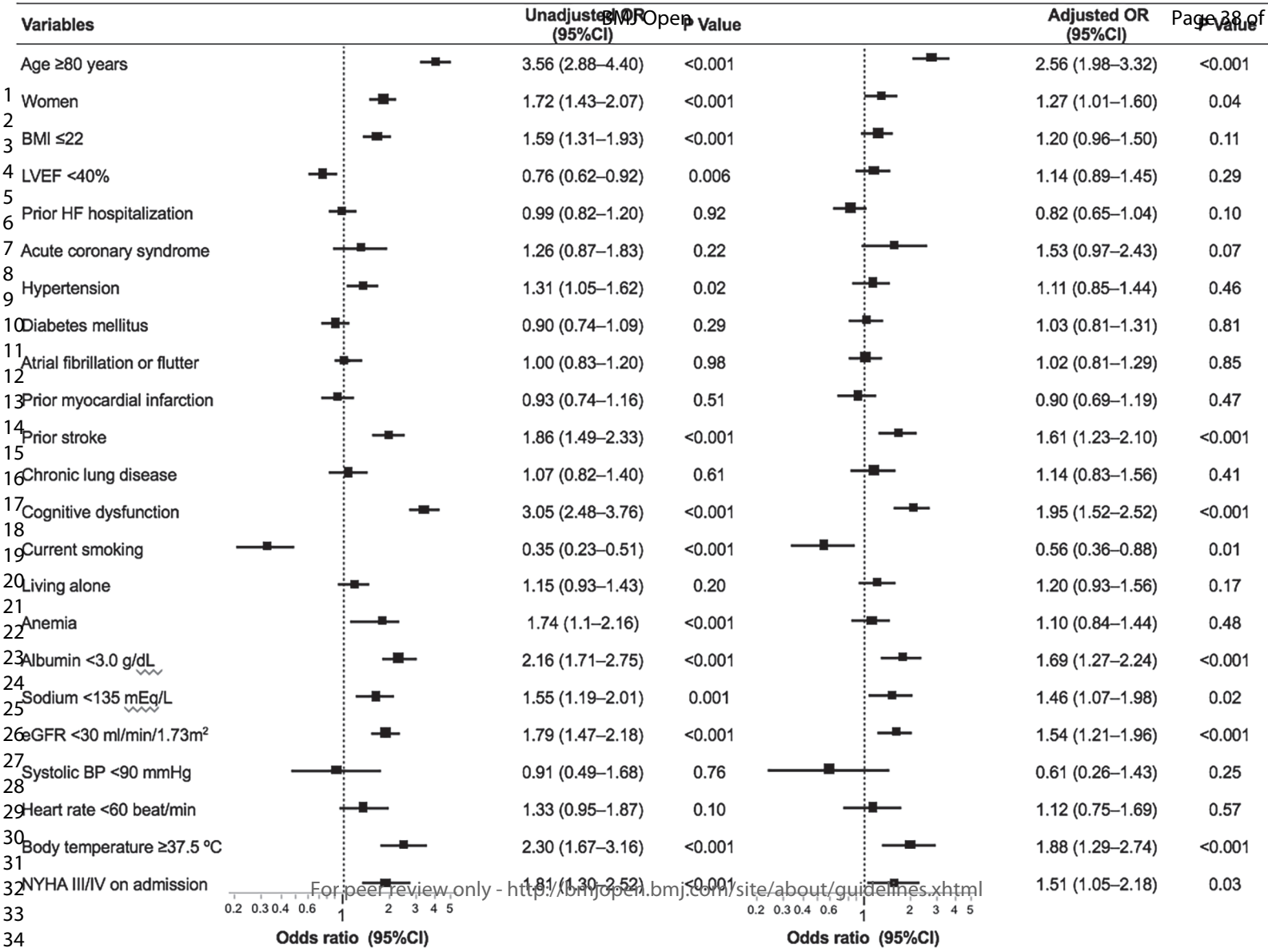
BMI=body mass index, HF=heart failure, BP=blood pressure, LVEF=left ventricular ejection fraction, HFrEF=heart failure with reduced ejection fraction, HFmrEF=heart failure with mid-range ejection fraction, HFpEF=heart failure with preserved ejection fraction, BNP=brain-type natriuretic peptide, NT-proBNP=N-terminal pro brain-type natriuretic peptide, eGFR=estimated glomerular filtration rate.

Table 2. In-hospital Management and Outcome

	Functional decline	No functional decline	P value
	N=528	N=3027	
In-hospital management			
Management in the emergency room			
Respiratory management			
Oxygen inhalation	295 (56)	1382 (46)	<0.001
NPPV	82 (16)	423 (14)	0.35
Intubation	11 (2.1)	53 (1.8)	0.60
Intravenous drugs within 24 hours after hospital presentation			
Inotropes	101 (19)	405 (13)	<0.001
Furosemide	446 (85)	2536 (84)	0.69
In-hospital clinical outcomes			
In-hospital adverse events			
Stroke	27 (5.1)	26 (0.9)	<0.001
Worsening heart failure	130 (25)	490 (16)	<0.001
Worsening renal function	244 (47)	992 (33)	<0.001
In-hospital infection	104 (20)	258 (8.5)	<0.001
Length of stay, day	21 [14–37]	15 [11–22]	<0.001
Clinical signs and symptoms at discharge			
Dyspnoea on exertion	206 (41)	731 (25)	<0.001
Oedema	89 (17)	320 (11)	<0.001
General malaise	152 (31)	388 (14)	<0.001
Loss of appetite	119 (24)	251 (8.7)	<0.001
Living place after discharge			
Home	247 (47)	2709 (90)	<0.001
Hospital	225 (43)	180 (6.0)	<0.001
Institution for the aged	50 (9.5)	114 (3.8)	<0.001
Other	4 (0.8)	17 (0.6)	0.59
Medications at discharge			
Number of drugs prescribed	8 (6–11)	9 (6–11)	0.12
Drugs			

Loop diuretics	428 (81)	2472 (82)	0.74
RAAS inhibitors	349 (66)	2320 (77)	<0.001
ACEI/ARB	242 (46)	1838 (61)	<0.001
MRA	208 (39)	1409 (47)	0.002
Beta blocker	287 (54)	2101 (69)	<0.001
Tolvaptan	76 (14)	299 (9.9)	0.002


KCHF registry
4056 patients hospitalized with ADHF
(Oct 2014-Mar 2016, 19 centers in Japan)
In-hospital death during index hospitalization (N=271)
Excluded (N=230)
No data about functional status (n = 99)
Bedridden before index hospitalization (n = 131)
Study population:
Patients discharged alive assessed for functional decline during hospitalization
3555 patients
Functional decline: 528 patients
No functional decline: 3027 patients



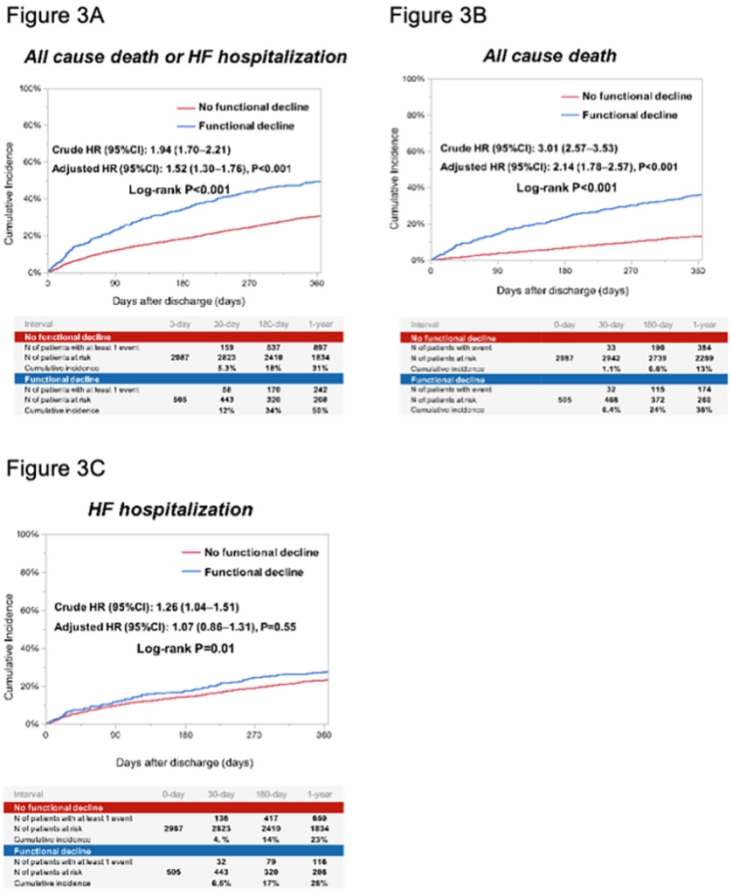


Figure 3. The Cumulative Incidences for the Primary Outcome Measure (A), for All-cause Death (B), and for HF Hospitalization (C) According to the Presence or Absence of Functional Decline.

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Supplementary Online Content

eTable 1. Clinical Factors associated with Functional Decline in the Entire Cohort in the Univariate and Multivariable Analyses

Variables	Unadjusted OR	P Value	Adjusted OR	P Value
Age ≥80 years	2.97 (2.50–3.52)	<0.001	2.25 (1.81–2.81)	<0.001
Women	1.45 (1.25–1.70)	<0.001	1.10 (0.90–1.34)	0.37
BMI ≤22	1.56 (1.32–1.83)	<0.001	1.19 (0.98–1.45)	0.08
LVEF <40%	1.04 (0.89–1.22)	0.61	1.23 (1.00–1.52)	0.048
Prior HF hospitalization	1.08 (0.92–1.27)	0.36	0.97 (0.79–1.19)	0.80
Acute coronary syndrome	1.56 (1.16–2.11)	0.003	1.73 (1.17–2.56)	0.006
Hypertension	1.00 (0.85–1.20)	0.95	0.97 (0.77–1.21)	0.76
Diabetes mellitus	0.86 (0.73–1.01)	0.06	0.88 (0.71–1.08)	0.22
Atrial fibrillation or flutter	0.97 (0.83–1.13)	0.67	0.91 (0.74–1.11)	0.33
Prior myocardial infarction	0.94 (0.78–1.13)	0.50	0.87 (0.69–1.11)	0.26
Prior stroke	1.73 (1.43–2.10)	<0.001	1.54 (1.21–1.94)	<0.001
Chronic lung disease	1.11 (0.89–1.39)	0.37	1.16 (0.89–1.52)	0.27
Cognitive dysfunction	2.91 (2.44–3.47)	<0.001	2.03 (1.63–2.53)	<0.001
Current smoking	0.37 (0.27–0.51)	<0.001	0.56 (0.38–0.82)	0.003
Living alone	1.05 (0.87–1.27)	0.62	1.19 (0.94–1.49)	0.14
Anaemia*	1.67 (1.39–1.98)	<0.001	1.07 (0.85–1.35)	0.56
Albumin <3.0 g/dL	2.30 (1.89–2.81)	<0.001	1.83 (1.44–2.33)	<0.001
Sodium <135 mEq/L	1.89 (1.53–2.33)	<0.001	1.68 (1.31–2.16)	<0.001
eGFR <30 ml/min/1.73m^2	2.01 (1.70–2.36)	<0.001	1.76 (1.43–2.17)	<0.001
Systolic BP <90 mmHg	2.01 (1.37–2.96)	<0.001	1.17 (0.67–2.05)	0.58
Heart rate <60 beat/min	1.07 (0.79–0.79)	0.66	1.03 (0.72–1.49)	0.87
Body temperature ≥37.5 ºC	2.26 (1.72–2.7)	<0.001	1.89 (1.35–2.63)	<0.001
NYHA III/IV on admission	2.17 (1.62–2.91)	<0.001	1.69 (1.21–2.35)	0.002

Values are number (%), mean ± SD, or median (interquartile range).

*Defined by the World Health Organization criteria (hemoglobin <12 g/dL for women and <13 g/dL for men).

BMI=body mass index, LVEF=left ventricular ejection, HF=heart failure, eGFR=estimated glomerular filtration rate, BP=blood pressure, NYHA=New York Heart Association, OR=odds ratio, CI=confidence interval.

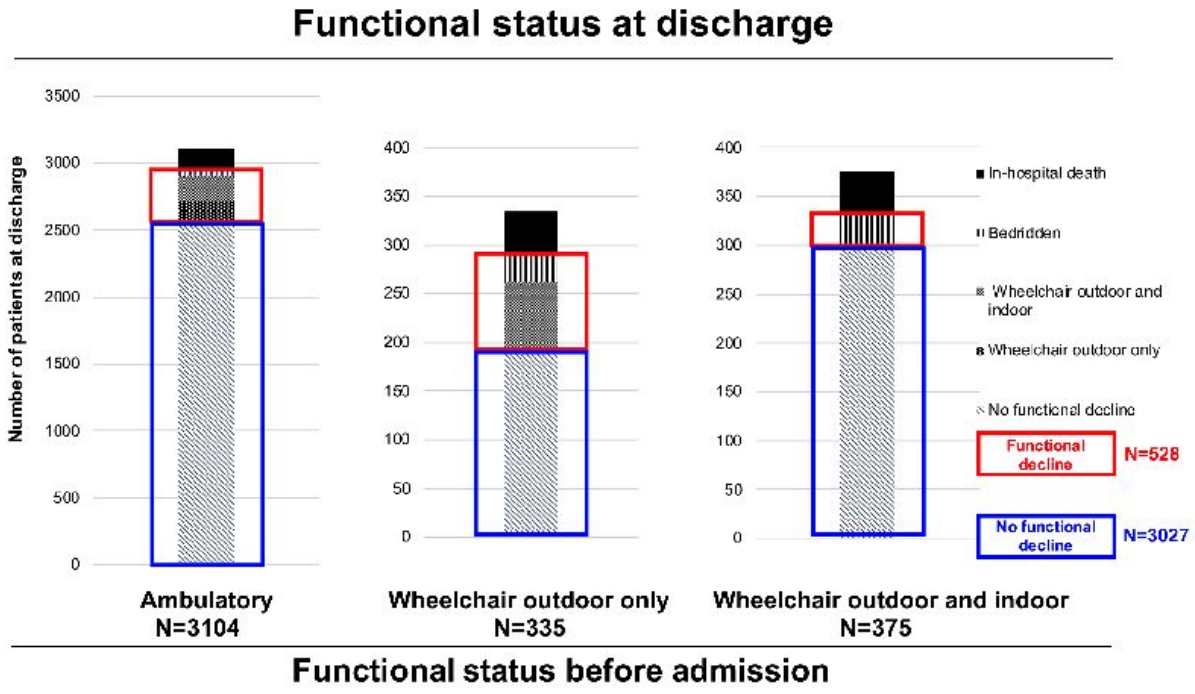
eTable 2. Clinical Outcomes in the Entire Cohort

Outcomes	Functional decline	No functional decline	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
	N of patients with event/N of patients at risk (Cumulative 1-year incidence [%])	N of patients with event/N of patients at risk (Cumulative 1-year incidence [%])				
All-cause death or HF hospitalization	242/505 (50)	897/2987 (31)	1.94 (1.70–2.21)	<0.001	1.5 (1.29–1.75)	<0.001
All-cause death	174/505 (36)	384/2987 (13)	3.01 (2.57–3.53)	<0.001	2.14 (1.78–2.57)	<0.001
HF hospitalization	116/505 (28)	659/2987 (23)	1.26 (1.04–1.51)	0.01	1.07 (0.86–1.31)	0.55

The number of patients with at least one event was counted through the 1-year follow-up period.

HF=heart failure, HR=hazard ratio, CI=confidence interval, HF=heart failure.

eFigure 1. The Details of Functional Decline during ADHF Hospitalization. Functional status at discharge according to functional status before admission is shown. ADHF=acute decompensated heart failure.



eFigure 2. Subgroup Analysis for the Association of Functional Decline with no Functional Decline on the Primary Outcome Measure. LVEF=left ventricular ejection fraction, HR=hazard ratio, CI=confidence interval.

	Functional decline	Non-functional decline	Adjusted HR (95% CI)	P value for interaction
	No. Events/No. at risk	No. Events/No. at risk		
Age, years				
<80	58/122	375/1604	1.48 (1.08–2.02)	0.45
≥80	185/390	527/1401	1.44 (1.21–1.71)	
Sex				
Female	122/286	383/1271	1.43 (1.15–1.78)	0.24
Male	121/226	519/1734	1.64 (1.33–2.03)	
LVEF, %				
<40	75/159	371/1136	1.30 (0.98–1.69)	0.09
≥40	168/351	528/1861	1.65 (1.37–1.98)	
Anaemia				
No	47/123	210/1068	1.70 (1.17–2.41)	0.12
Yes	196/389	691/1931	1.44 (1.22–1.70)	
Albumin <3.0 g/dL				
No	169/394	760/2586	1.38 (1.16–1.64)	0.09
Yes	67/108	117/182	1.95 (1.40–2.69)	
Body temperature ≥37.5 ºC				
No	211/433	815/2712	1.51 (1.29–1.76)	0.89
Yes	25/56	42/153	1.55 (0.84–2.78)	
Oedema at discharge				
No	184/408	739/2597	1.42 (1.20–1.68)	0.28
Yes	51/88	128/318	1.86 (1.23–2.80)	
General malaise at discharge				
No	142/320	690/2398	1.38 (1.15–1.67)	0.48
Yes	83/149	151/385	1.62 (1.18–2.21)	

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Risk factors and clinical outcomes of functional decline during acute decompensated heart failure hospitalization: an observational study

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Heart failure < CARDIOLOGY, Adult cardiology < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY

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Risk factors and clinical outcomes of functional decline during acute decompensated heart failure hospitalization: an observational study

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Abstract

Objective: To investigate the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in patients with acute decompensated heart failure (ADHF) hospitalization.

Design: Prospective cohort study between October 1, 2014, and March 31, 2016.

Setting: A physician-initiated multicentre study of consecutive patients admitted for ADHF into 19 hospitals throughout Japan.

Participants: Among 3555 patients hospitalized for ADHF (median age [IQR], 80 [71-86] years; 1572 [44%] women), functional decline during the index hospitalization occurred in 528 patients (15%).

Primary and secondary outcomes: The primary outcome measure was a composite of all-cause death or heart failure hospitalization after discharge. The secondary outcome measures were all-cause death, heart failure hospitalization, and a composite of all-cause death or all-cause hospitalization.

Results: The independent risk factors for functional decline included age ≥80 years (OR 2.56; 95% CI 1.98–3.32), women (OR 1.27; 95% CI 1.01–1.60), prior stroke (OR 1.61; 95% CI 1.23–2.10), dementia (OR 1.95; 95% CI 1.52–2.52), elevated body temperature (OR 1.88;

95% CI 1.29–2.74), hyponatremia (OR 1.46; 95% CI 1.07–1.98), decreased albumin levels (OR 1.69; 95% CI 1.27–2.24), renal dysfunction (OR 1.54; 95% CI 1.21–1.96), and New York Heart Association class III or IV on admission (OR 1.51; 95% CI 1.05–2.18) after multivariable adjustment. The cumulative 1-year incidence of the primary outcome in the functional decline group was significantly higher than that in the no functional decline group (50% vs. 31%, log-rank P<0.001). After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR 1.39; 95% CI 1.18–1.62; P<0.001).

Conclusions: Independent risk factors of functional decline in ADHF patients were related to both frailty and severity of heart failure. Functional decline during ADHF hospitalization was associated with unfavourable post-discharge outcomes.

Trial Registration: https://clinicaltrials.gov/ct2/show/NCT02334891 (NCT02334891) and https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000017241 (UMIN000015238)

Strengths and limitations of this study

- This study is the first large-scale contemporary multicentre observational study reporting the prevalence of functional decline in patients hospitalized for acute decompensated heart failure (ADHF).
- The data of this study were prospectively collected on consecutive patients who had hospital admission due to ADHF in the real-world clinical practice in Japan.
- This study examines the risk factors of functional decline in patients hospitalized for ADHF, and whether functional decline during the index hospitalization was associated with worse post-discharge outcomes.
- We did not collect data regarding on-site and outpatient rehabilitation and nutritional support.

Introduction

Functional decline in hospitalized patients is a complex and dynamic process [1–3]. Functional decline during hospitalization was reported to occur in approximately 30-50% of patients hospitalized for acute medical illness [2,4,5]. In the rapidly aging societies, the number of patients hospitalized for acute decompensated heart failure (ADHF) is increasing, and ADHF has become the leading cause of hospitalization due to acute medical illness. In older patients, functional decline associated with hospitalization often leads to subsequent inability to live actively and independently.

However, there is a scarcity of data regarding the risk factors of functional decline in patients hospitalized for ADHF. Identifying high-risk patients for functional decline during hospitalization would be useful for its prevention. Furthermore, no previous study focused on subsequent clinical outcomes in patients with functional decline during hospitalization. Therefore, we sought to clarify the risk factors for functional decline during hospitalization in patients with ADHF and to compare the 1-year clinical outcomes between the 2 groups of patients with and without functional decline during the hospitalization for ADHF in a large Japanese observational database of hospitalized patients for ADHF in the real-world clinical practice.

Methods

Study Design, Setting, and Population

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled consecutive patients who were hospitalized for ADHF for the first time between October 1, 2014, and March 31, 2016. These patients were admitted into 19 secondary and tertiary hospitals, including rural and urban as well as large and small institutions, throughout Japan. The study protocol was approved by the institutional review board of Kyoto University (approval number: E2311) and each participating centre. A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating centre because the study met the conditions of the Japanese ethical guidelines for epidemiological study and the US policy for protecting human research participants.[6,7] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The details of the KCHF study design and patient enrolment are described elsewhere.[8–11] Briefly, we enrolled all patients with ADHF, as defined by the modified Framingham criteria, who were admitted to the participating hospitals and patients who

underwent heart failure–specific treatment involving intravenous drugs within 24 hours after hospital presentation. Patient records were anonymized before analysis. Data analysis was conducted from August 2018 to October 2018.

Among 4056 patients enrolled in the KCHF registry, 3785 patients were discharged alive after hospitalization for ADHF. Clinical follow-up data were collected in October 2017. The attending physicians or research assistants at each participating hospital collected clinical events after the index hospitalization from hospital charts or by contacting patients, their relatives, or their referring physicians with consent. The present analysis had 2 objectives. First, we sought to clarify the risk factors for functional decline during hospitalization of ADHF patients. Second, we sought to compare the 1-year clinical outcomes between the 2 groups of patients with and without functional decline during the hospitalization for ADHF. Among 4056 patients enrolled in the KCHF registry, the current study population consisted of 3555 patients who were discharged alive and were assessed for functional decline during hospitalization, excluding 271 patients who died during the index hospitalization, 99 patients whose functional status before admission and/or at discharge was not available, and 131 patients who were bedridden before index hospitalization (Figure 1). The long-term follow-up was censored at 1-year. The primary outcome measure in the current analysis was a

composite of all-cause death or heart failure hospitalization at 1-year. The secondary outcome measures were all-cause death, heart failure hospitalization, and a composite of all-cause death or all-cause hospitalization at 1-year.

Definitions

Physical activity before admission and at discharge 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 stick), use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state.[8] Functional decline was defined as the decline of at least one stage on physical activity at discharge compared with pre-admission status. In-hospital worsening heart failure was defined as additional intravenous drug administration for heart failure, haemodialysis, or mechanical circulatory or respiratory support, occurring >24 hours after therapy initiation.[12] In-hospital worsening renal function was defined as >0.3 mg/dL increase in serum creatinine levels during the index hospitalization.[13–15] Detailed definitions of baseline clinical characteristics including the signs and symptoms of heart failure were described previously.[9] Missing values were presented in eTable 1.

Statistical Analysis

Categorical variables were presented as numbers with percentages and compared using χ^2 test. Continuous variables were expressed as the mean with standard deviation or median with 25th to 75th percentiles, and compared using the Student's *t* test when normally distributed or Wilcoxon rank-sum test when not normally distributed.

We compared baseline characteristics and clinical outcomes based on the presence or absence of functional decline during the index hospitalization. A multivariable logistic regression model was developed to identify clinical characteristics associated with an increased risk for functional decline. We used 23 clinically relevant factors listed in Table 1 as potential independent risk factors in multivariable logistic regression models and estimated the odd ratios (ORs) and 95% confidence intervals (CIs). We used the Kaplan-Meier method to estimate the cumulative 1-year incidences of the outcome measures and assessed the differences with the log-rank test. We expressed the associations of the functional decline group with the no functional decline group for all outcome measures as hazard ratios (HRs) with 95% CIs by multivariable Cox proportional hazard models incorporating 29 clinically relevant risk-adjusting variables indicated in Table 1. We also conducted subgroup analyses stratified by age, sex, LVEF, anaemia, albumin levels, body temperature, and the symptomatic status at discharge (oedema and general malaise at discharge). In the

multivariable analysis and subgroup analyses, continuous variables were dichotomized by clinically meaningful reference values or median values; age ≥80 years based on the median value, LVEF <40% based on the heart failure guideline of LVEF classification [16], BMI ≤22 kg/m^2, renal dysfunction (eGFR <30 ml/min/1.73m^2) based on CKD grade, decreased albumin levels (serum albumin <3.0 g/dL), hyponatremia (serum sodium <135 mEq/L), elevated body temperature (body temperature ≥37.5℃) based on the cut-off value in metabolic syndrome [17].

We performed an additional analysis using the data including those patients who died during the index hospitalization and those who were bedridden before the index hospitalization, and evaluated the factors associated with functional decline or in-hospital mortality by constructing the multivariable adjusted Cox models. All statistical analyses were conducted by a physician (H.Y.) and a statistician (T.M.) with JMP 13.0 or SAS 9.4 (both SAS Institute Inc, Cary, NC). Two-tailed P-values less than 0.05 were considered statistically significant.

Patient and public involvement

No patient involved.

Results

Baseline Clinical Characteristics

Among 3555 study patients, physical activity before admission included ambulatory in 2949 patients (83%), wheelchair outdoor only in 272 patients (7.7%), and wheelchair outdoor and indoor in 334 patients (9.4%). At hospital discharge, functional decline was observed in 420 patients (14%) who were ambulatory before admission, in 80 patients (29%) who had used wheelchair outdoor only, and in 28 patients (8.4%) who had used wheelchair outdoor and indoor. Consequently, decline in functional status was observed in 528 patients (15%; functional decline group), while functional decline was not observed in 3027 patients (85%; no functional decline group) (eFigure 1). Wheelchair outdoor only before admission were more prevalent in the functional decline group than in the no functional decline group; however, 80% of patients in the functional decline group were ambulatory before admission (Table 1).

Regarding the baseline clinical characteristics, the patients in the functional decline group were older and had a higher prevalence of hypertension, prior stroke, renal dysfunction, dementia, malignancy, anaemia, decreased albumin levels, and hyponatremia (Table 1). There were no significant differences in previous heart failure hospitalization,

atrial fibrillation or flutter, previous myocardial infarction, chronic lung disease, and living alone status as a social background between the 2 groups (Table 1). The functional decline group was more likely to have a valvular aetiology, lower blood pressure, lower heart rate, higher levels of brain natriuretic peptide (BNP) or N-terminal portion of proBNP (NT-proBNP), and a higher LVEF (Table 1). The proportion of patients who achieved relief of signs and symptoms on admission after the treatment in the emergency room was not significantly different between the 2 groups (14% vs. 16%, P=0.25).

Risk Factors for Functional Decline

Among the baseline characteristics and status at hospital presentation, the following independent risk factors for functional decline during hospitalization were identified by the multivariable logistic regression analysis: age ≥80 years (OR 2.56; 95% CI 1.98–3.32), women (OR 1.27; 95% CI 1.01–1.60), prior stroke (OR 1.61; 95% CI 1.23–2.10), dementia (OR 1.95; 95% CI 1.52–2.52), elevated body temperature (OR 1.88; 95% CI 1.29–2.74), hyponatremia (OR 1.46; 95% CI 1.07–1.98), decreased albumin levels (OR 1.69; 95% CI 1.27–2.24), eGFR <30 ml/min/1.73m^2 (OR 1.54; 95% CI 1.21–1.96), and New York Heart Association (NYHA) class III or IV on admission (OR 1.51; 95% CI 1.05–2.18) (Figure 2 and eTable 2).

In-hospital adverse events and status at discharge

The median length of hospital stay was longer in the functional decline group than in the no functional decline group (21 days vs. 15 days, P <0.001). Regarding the in-hospital adverse events, the prevalence of worsening heart failure, worsening renal function, and stroke was higher in the functional decline group than in the no functional decline group (Table 2). The proportion of patients with symptoms such as oedema and general malaise at discharge was higher in the functional decline group than in the no functional decline group (Table 1). Consequently, the proportion of patients in the functional decline group discharged to home was also lower (47% vs. 90%, P <0.001). Regarding medical treatment at discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI or ARB), and beta blocker were less often prescribed in the functional decline group than in the no functional decline group (Table 1).

Long-term outcomes: functional decline vs. no functional decline groups

Follow-up rate at 1-year was 96%. The cumulative 1-year incidence of the primary outcome measure (a composite of all-cause death or heart failure hospitalization) in the functional decline group was significantly higher than that in the no functional decline group (49% vs. 31%, log-rank P<0.001) (Figure 3). After adjusting for baseline characteristics, the

higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR, 1.39; 95%CI, 1.18–1.62; P<0.001) (Figure 3 and eTable 3). The cumulative 1-year incidence of all-cause death was also significantly higher in the functional decline group than in the no functional decline group. Even after adjusting confounders, the excess mortality risk of the functional decline group relative to the no functional decline group remained significant (Figure 3 and eTable 3). The cumulative 1-year incidence of heart failure hospitalization was also significantly higher in the functional decline group than in the no functional decline group. However, the adjusted risk of the functional decline group relative to the no functional decline group for heart failure hospitalization was no longer significant (Figure 3 and eTable 3). The cumulative 1-year incidence of a composite of all-cause death or all-cause hospitalization was significantly higher in the functional decline group than in the no functional decline group. After adjusting confounders, the higher risk of the functional decline group relative to the no functional decline group remained significant (Figure 3 and eTable 3). In the subgroup analyses, there were no interactions between those subgroup factors and the association of functional decline with the primary outcome measure (eFigure 2).

Additional analysis on the risk factors for functional decline or in-hospital mortality

The risk factors for functional decline or in-hospital mortality in a total of 4056 patients were similar to the risk factors for functional decline. LVEF <40% (OR, 1.23; 95% CI, 1.00–1.52) and acute coronary syndrome (OR, 1.73; 95% CI, 1.17–2.56) that were not included in the risk factors for functional decline emerged as the risk factors for functional decline or in-hospital mortality. Meanwhile, among the risk factors for functional decline, women (OR, 1.10; 95% CI, 0.90–1.34) was not included in the risk factors for functional decline or in-hospital mortality (Figure 2 and eTable 2).

Discussion

The main findings of the present study investigating the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in patients with ADHF hospitalization were as follows; 1) Functional decline during ADHF hospitalization occurred in 15% of patients, and 80% of those with functional decline were ambulatory before admission; 2) The independent baseline risk factors associated with functional decline included age ≥80 years, women, prior stroke, dementia, elevated body temperature, hyponatremia, decreased albumin levels, eGFR <30 ml/min/1.73m^2, and NYHA class III or IV; 3) Functional decline during the index hospitalization was associated with

higher long-term risk for a composite of all-cause death or heart failure hospitalization.

This is the first large-scale contemporary multicentre study reporting the prevalence of functional decline in patients hospitalized for ADHF. Of note, we identified the severity of symptoms or patient status specific for heart failure was associated with functional decline independent of well-known factors in acute medical illness [18–20]. Functional decline is an inevitable consequence in aged people, but hospitalization accelerates the decline [20–22]. Functional declines have been found to be related not only to impairment of independence and quality of life (QOL), but also to increased health service use, higher risk for institutionalization, and higher risk for mortality [23–27]. Indeed, in the present study, the proportion of patients discharged to home was lower in the functional decline group than in the no functional decline group, suggesting impaired QOL after discharge. Also, the long-term mortality was worse in the functional decline group than in the no functional decline group. Therefore, it is important to recognize risk factors of functional decline. In previous studies of hospitalized patients with acute medical illness, the predictors of functional decline in hospitalized elderly patients were older age, admission diagnosis, lower functional status, impaired cognitive status, comorbidities, and length of hospital stay.[18–20] These findings were confirmed in the setting of ADHF in our present study. In addition, findings specific for

ADHF such as the dyspnoea or hyponatremia was associated with functional decline, which were also reported to be the risk factors for in-hospital mortality in ADHF [28]. The prevalence of oedema and general malaise at discharge was higher in the functional decline group. Early achievement of successful ADHF treatment might reduce the risk of functional decline, although the present observational study could not address the cause-effect relationship between the functional decline and the symptomatic status at discharge.

There might be several possible strategies to prevent functional decline during ADHF hospitalization. The first is the early improvement of hemodynamic status to avoid worsening heart failure. The prevalence of worsening heart failure was higher in the functional decline group. As functional decline associated with hospitalization begins within 48 hours of admission, early improvement of heart failure to reduce the incidence of hospitalization-associated disability is one of the main goals of care.[28] Second, it would be important to be adequately aware high-risk patients to make aggressive intervention for preventing functional decline. We identified the risk factors among the baseline characteristics in ADHF patients. In addition, the adverse events during hospitalization may be tightly related to the functional decline. Stroke is one of causes of functional decline and observed in 5.1% of patients with functional decline. Third, a strategy for the prevention of

functional decline might be the seamless rehabilitation and comprehensive geriatric management through a multidisciplinary team approach.[29–32] In addition, the subgroup analysis showed that there were no interactions between those subgroup factors and the association of functional decline with the primary outcome measure. Thus, prevention of functional decline would have an impact on improving outcomes in all of the patients with ADHF. One possible strategy could be immediate, tailored physical function rehabilitation during and after heart failure hospitalization.[33]

Limitations

This study has several limitations. First, we adopted simple classification of functional status as ambulatory, use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state based on the definition of Japanese long-term care insurance. The categorization scheme is an easy to understand but coarse measure with very large gradations inherent in each single stage and therefore very likely substantially underestimated the prevalence of meaningful functional decline. Second, we did not collect data regarding on-site and outpatient rehabilitation and nutritional support. However, a team-based approach for heart failure patients was adapted in all the participating centres in the present study. Third, we did not include the status at discharge or adverse in-hospital events in the analysis

for the risk factor for functional decline, because the cause-effect relationship was not clear. Fourth, data on post-discharge medication and change of functional status after discharge from the index hospitalization were not collected, and not analysed in the analysis for the long-term outcomes. Fifth, as with any observational study, the possibility of selection bias and residual confounding cannot be excluded, although we adjusted for 29 variables as most conceivable confounders.

Conclusions

Independent risk factors of functional decline in ADHF patients were related to both frailty and severity of heart failure. Functional decline during ADHF hospitalization was associated with unfavourable post-discharge outcomes.

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Disclosures

None

Author Contributions

Drs Yaku and T. Kato had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yaku, T. Kato, Morimoto, Tamaki, Ozasa, Yamamoto, Kitai, M. Kato, Kimura.

Acquisition, analysis, or interpretation of data: Yaku, T. Kato, Morimoto, Inuzuka, Tamaki, Yoshikawa, Ikeda, Furukawa, Kuwahara.

Drafting of the manuscript: Yaku, T. Kato, Kimura.

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Statistical analysis: Yaku, T. Kato, Morimoto.

Administrative, technical, or material support: T. Kato, Sato, Kimura.

Supervision: Inuzuka, Ozasa, Kitai, Furukawa, Nakagawa, Sato, Kuwahara, Kimura.

Ethics approval

The study was approved by the Institutional Review Boards of Kyoto University Graduate School of Medicine (approval number: E2311), Shiga General Hospital (approval number: 20141120-01), Tenri Hospital (approval number: 640), Kobe City Medical Centre General Hospital (approval number: 14094), Hyogo Prefectural Amagasaki General Medical Centre

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Data sharing

All data relevant to the study are included in the article or uploaded as supplementary information. No additional data available.

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Figure legends

Figure 1. **Patient flowchart.** KCHF=Kyoto Congestive Heart Failure, ADHF=acute decompensated heart failure.

Figure 2. Clinical factors associated with functional decline during hospitalization in the univariate and multivariable logistic regression models. BMI=body mass index, LVEF=left ventricular ejection, HF=heart failure, eGFR=estimated glomerular filtration rate, BP=blood pressure, NYHA=New York Heart Association, OR=odds ratio, CI=confidence interval.

Figure 3. **The Cumulative incidences for the primary outcome measure (A), for all-cause death (B), for HF hospitalization (C), and for a composite of all-cause death or all-cause hospitalization (D) according to the presence or absence of functional decline.** HF=heart failure, HR=hazard ratio, CI=confidence interval.

Table 1. Patient Characteristics

	Functional decline	No functional decline	P value
	N=528	N=3027	
Clinical characteristics			
Age, years	85 [80–89]	79 [70–85]	<0.001
Age ≥80 years*†	399 (76)	1407 (46)	<0.001
Women*†	294 (56)	1278 (42)	<0.001
BMI, kg/m^2	22.0±4.0	23.1±4.5	<0.001
BMI ≤22 kg/m^2*†	269 (55)	1281 (44)	<0.001
Medical history			
Prior heart failure hospitalization*†	186 (36)	1077 (36)	0.92
Atrial fibrillation or flutter	220 (42)	1263 (42)	0.98
Hypertension*†	406 (77)	2174 (72)	0.02
Diabetes mellitus*†	187 (35)	1145 (38)	0.29
Prior myocardial infarction*†	112 (21)	681 (23)	0.51
Prior stroke*†	125 (24)	432 (14)	<0.001
Current smoking*†	28 (5.5)	425 (14)	<0.001
Malignancy	97 (18)	419 (14)	0.006
Chronic lung disease*†	41 (7.8)	247 (8.2)	0.76
Dementia*†	175 (33)	423 (14)	<0.001
Social backgrounds at admission			
Poor medical adherence	100 (19)	498 (16)	0.16
Living alone*†	127 (24)	652 (22)	0.20
Public assistance	24 (4.6)	186 (6.1)	0.14
Functional status before admission			
Ambulatory	420 (80)	2529 (84)	0.02
Use of wheelchair [outdoor only]	80 (15)	192 (6.3)	<0.001
Use of wheelchair [outdoor and indoor]	28 (5.3)	306 (10)	<.0001
Origin			
Ischemic	134 (25)	820 (27)	0.41
Acute coronary syndrome*†	36 (6.8)	166 (5.5)	0.22
Hypertensive	131 (25)	754 (25)	0.96

Valvular	124 (23)	565 (19)	<0.001
Cardiomyopathy	54 (10)	492 (16)	<0.001
Vital signs and symptoms at presentation			
BP, mmHg			
Systolic BP	144±32	149±35	0.003
Systolic BP ≥140 mmHg	275 (53)	1741 (58)	0.03
Systolic BP <90 mmHg*†	12 (2.3)	76 (2.5)	0.76
Diastolic BP	81±23	86±24	<0.001
Heart rate, beat/min	93±27	96±28	0.001
Heart rate <60 beat/min*†	44 (8.5)	195 (6.5)	0.11
Body temperature, ºC	36.6±0.7	36.5±0.6	<0.001
Body temperature ≥37.5ºC*†	58 (11)	154 (5.3)	<0.001
Rhythms at presentation			
Sinus rhythm	280 (53)	1715 (57)	0.12
Atrial fibrillation or flutter*†	198 (38)	1085 (36)	0.47
NYHA class III or IV*†	482 (92)	2598 (73)	<0.001
Tests at admission			
LVEF	48±16	46±16	0.02
HFrEF (EF<40%)*†	167 (32)	1148 (38)	0.006
HFmrEF (EF 40–49%)	117 (22)	566 (19)	0.06
HFpEF (EF ≥50%)	242 (46)	1305 (43)	0.24
Haemoglobin, g/dL	11.0±2.1	11.7±2.4	<0.001
Anaemia*†‡	401 (76)	1946 (64)	<0.001
BNP, pg/ml	782 [448–1410]	687 [375–1214]	<0.001
NT-proBNP, pg/ml	10795 [3450–18000]	5416 [2629–11438]	0.001
Creatinine, mg/dL	1.2 [0.8–1.6]	1.1 [0.8–1.6]	0.21
eGFR, ml/min/1.73m^2	38 [24–54]	46 [30–62]	<0.001
eGFR <30 ml/min/1.73m^2*†	195 (37)	747 (25)	<0.001
Blood urea nitrogen, mg/dL	28 (20–39)	23 (17–33)	<0.001
Albumin, g/dL	3.3±0.5	3.5±0.5	<0.001
Albumin <3.0 g/dL*†	112 (22)	332 (11)	<0.001
Sodium, mEq/L	138±4.7	139±4.1	<0.001
Sodium <135 mEq/L*†	83 (16)	325 (11)	0.001

Potassium, mEq/L	4.3±0.8	4.2±0.6	0.03
Clinical signs and symptoms at discharge			
Oedema†	89 (17)	320 (11)	<0.001
General malaise†	152 (31)	388 (14)	<0.001
Medications at discharge			
Number of drugs prescribed	8 (6–11)	9 (6–11)	0.12
Loop diuretics†	428 (81)	2472 (82)	0.74
ACEI or ARB†	242 (46)	1838 (61)	<0.001
MRA†	208 (39)	1409 (47)	0.002
Beta blocker†	287 (54)	2101 (69)	<0.001
Tolvaptan	76 (14)	299 (9.9)	0.002
Functional status at discharge			
Ambulatory	0	2682 (89)	<0.001
Use of wheelchair [outdoor only]	184 (35)	160 (5.3)	<0.001
Use of wheelchair [outdoor and indoor]	261 (49)	185 (6.1)	<.0001
Bedridden	83 (16)	0	<0.001
Living place after discharge			
Home	247 (47)	2709 (90)	<0.001
Hospital	225 (43)	180 (6.0)	<0.001
Institution for the aged	50 (9.5)	114 (3.8)	<0.001
Other	4 (0.8)	17 (0.6)	0.59

Abbreviations: BMI, body mass index; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; BNP, brain-type natriuretic peptide; NT-proBNP, N-terminal-proBNP; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Continuous variables were presented as mean ± SD or median with [interquartile range]. Categorical variables were presented as number (percentage).

* Risk-adjusting variables were selected for multivariable logistic regression models.

† Risk-adjusting variables were selected for multivariable Cox proportional hazard models.

‡ Defined by the World Health Organization criteria (haemoglobin <12 g/dL for women and <13 g/dL for men).

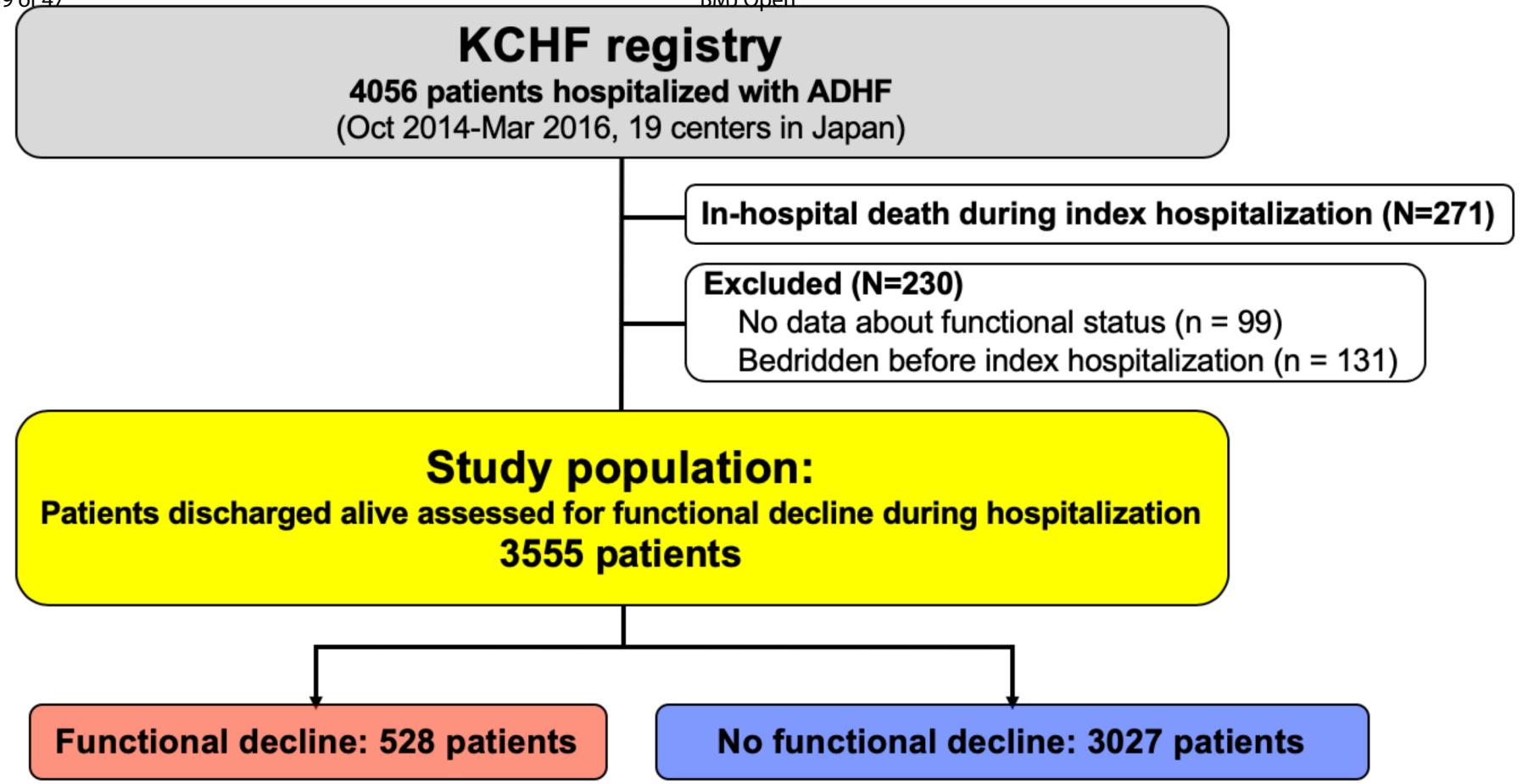
1

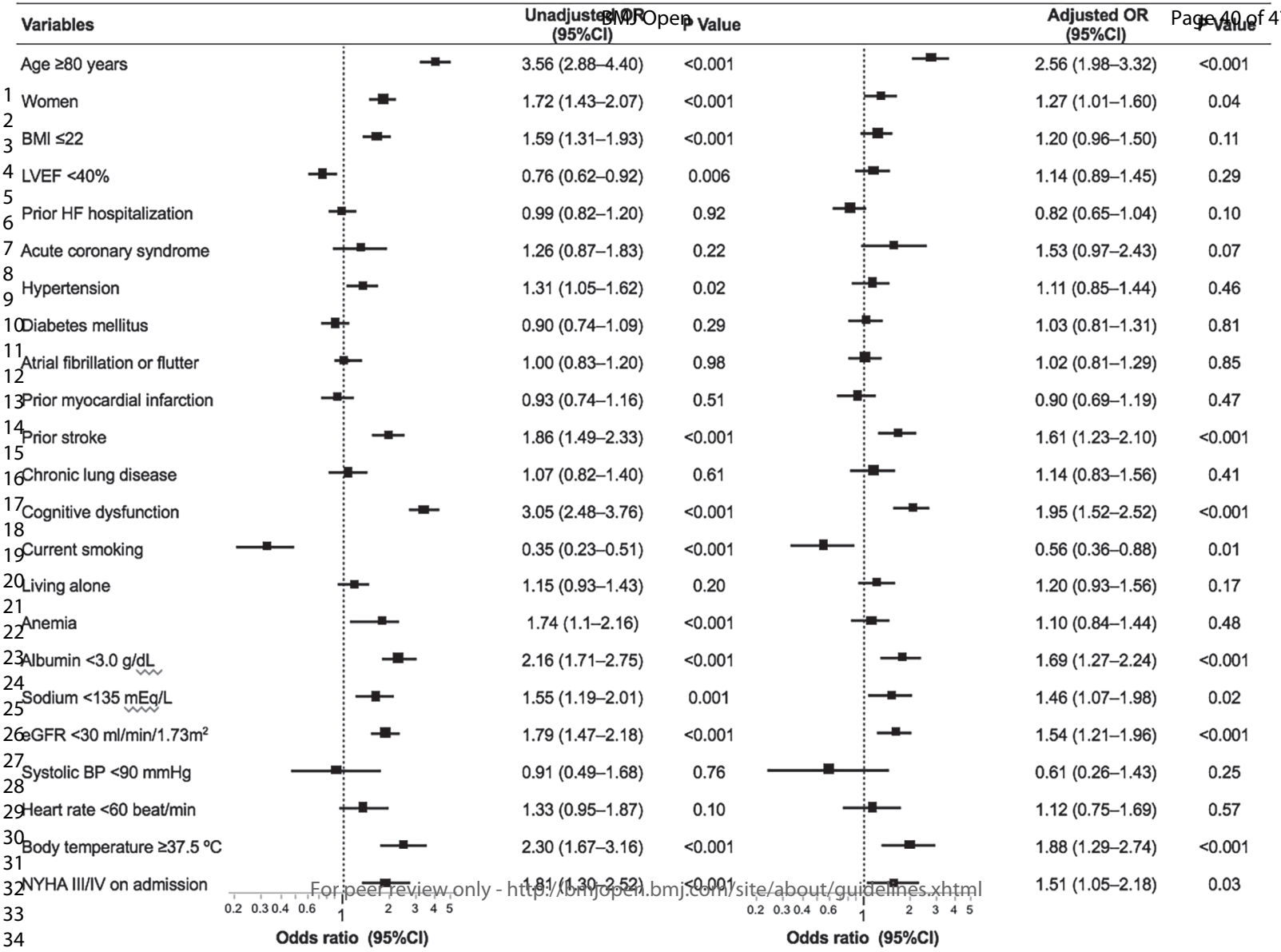
Table 2. In-hospital Management and Outcome

	Functional decline	No functional decline	P value
	N=528	N=3027	
In-hospital management			
Management in the emergency room			
Respiratory management			
Oxygen inhalation	295 (56)	1382 (46)	<0.001
NIPPV	82 (16)	423 (14)	0.35
Intubation	11 (2.1)	53 (1.8)	0.60
Intravenous drugs within 24 hours after hospital presentation			
Inotropes	101 (19)	405 (13)	<0.001
Furosemide	446 (85)	2536 (84)	0.69
In-hospital clinical outcomes			
In-hospital adverse events			
Stroke	27 (5.1)	26 (0.9)	<0.001
Worsening heart failure	130 (25)	490 (16)	<0.001
Worsening renal function	244 (47)	992 (33)	<0.001
In-hospital infection	104 (20)	258 (8.5)	<0.001
Length of stay, day	21 [14–37]	15 [11–22]	<0.001

Abbreviations: NIPPV, non-invasive intermittent positive pressure ventilation.

1


KCHF registry
4056 patients hospitalized with ADHF
(Oct 2014-Mar 2016, 19 centers in Japan)
In-hospital death during index hospitalization (N=271)
Excluded (N=230)
No data about functional status (n = 99)
Bedridden before index hospitalization (n = 131)
Study population:
Patients discharged alive assessed for functional decline during hospitalization
3555 patients
Functional decline: 528 patients
No functional decline: 3027 patients



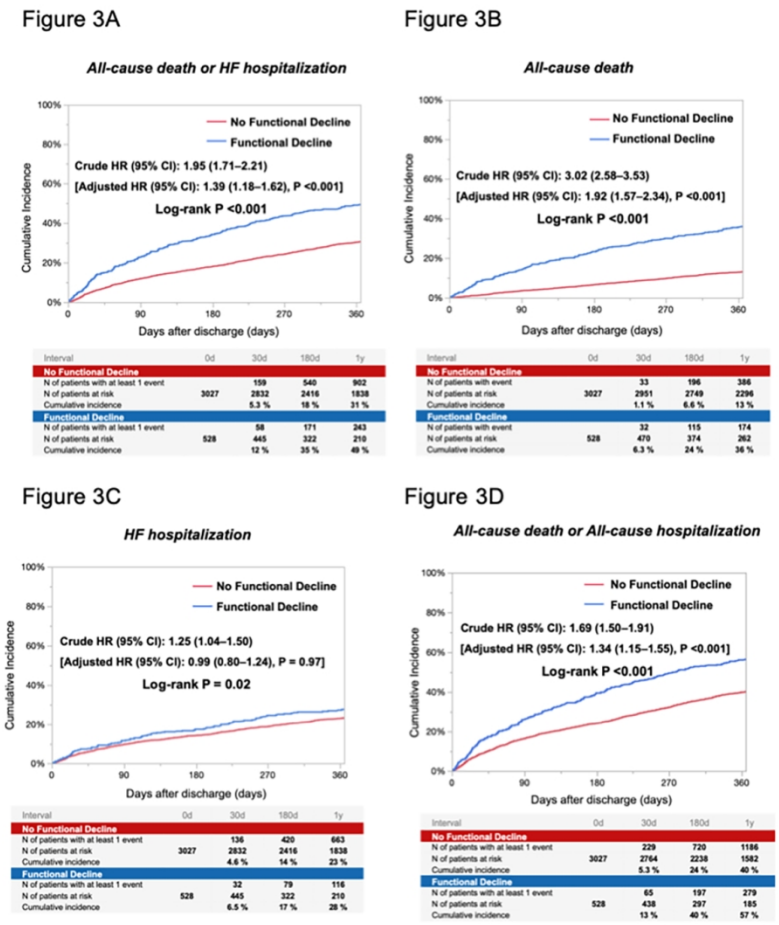


Figure 3. The Cumulative incidences for the primary outcome measure (A), for all-cause death (B), for HF hospitalization (C), and for a composite of all-cause death or all-cause hospitalization (D) according to the presence or absence of functional decline.

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Supplementary Online Content

eTable 1. Number of missing values in the entire cohort

	Entire Cohort (N=3555)	
	Number	**Rate (%)**
Tests at admission		
BNP or NT-proBNP *	46	1.24
Serum creatinine	6	0.16
eGFR	6	0.16
Blood urea nitrogen	11	0.30
Albumin	110	2.96
Sodium	13	0.35
Potassium	13	0.35
Haemoglobin	6	0.16

* BNP values were reported for 1887 patients in the matched cohort and 3394 patients in the entire cohort; NT-proBNP values were reported for 181 patients in the matched cohort and 323 patients in the entire cohort.
Abbreviation: BNP, brain-type natriuretic peptide; NT-proBNP, N-terminal-proBNP; eGFR, estimated glomerular filtration rate.

eTable 2. Clinical factors associated with functional decline in the entire cohort in the univariate and multivariable analyses

Variables	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age ≥80 years	2.97 (2.50–3.52)	<0.001	2.25 (1.81–2.81)	<0.001
Women	1.45 (1.25–1.70)	<0.001	1.10 (0.90–1.34)	0.37
BMI ≤22	1.56 (1.32–1.83)	<0.001	1.19 (0.98–1.45)	0.08
LVEF <40%	1.04 (0.89–1.22)	0.61	1.23 (1.00–1.52)	0.048
Prior HF hospitalization	1.08 (0.92–1.27)	0.36	0.97 (0.79–1.19)	0.80
Acute coronary syndrome	1.56 (1.16–2.11)	0.003	1.73 (1.17–2.56)	0.006
Hypertension	1.00 (0.85–1.20)	0.95	0.97 (0.77–1.21)	0.76
Diabetes mellitus	0.86 (0.73–1.01)	0.06	0.88 (0.71–1.08)	0.22
Atrial fibrillation or flutter	0.97 (0.83–1.13)	0.67	0.91 (0.74–1.11)	0.33
Prior myocardial infarction	0.94 (0.78–1.13)	0.50	0.87 (0.69–1.11)	0.26
Prior stroke	1.73 (1.43–2.10)	<0.001	1.54 (1.21–1.94)	<0.001
Chronic lung disease	1.11 (0.89–1.39)	0.37	1.16 (0.89–1.52)	0.27
Dementia	2.91 (2.44–3.47)	<0.001	2.03 (1.63–2.53)	<0.001
Current smoking	0.37 (0.27–0.51)	<0.001	0.56 (0.38–0.82)	0.003
Living alone	1.05 (0.87–1.27)	0.62	1.19 (0.94–1.49)	0.14
Anaemia*	1.67 (1.39–1.98)	<0.001	1.07 (0.85–1.35)	0.56
Albumin <3.0 g/dL	2.30 (1.89–2.81)	<0.001	1.83 (1.44–2.33)	<0.001
Sodium <135 mEq/L	1.89 (1.53–2.33)	<0.001	1.68 (1.31–2.16)	<0.001
eGFR <30 ml/min/1.73m^2	2.01 (1.70–2.36)	<0.001	1.76 (1.43–2.17)	<0.001
Systolic BP <90 mmHg	2.01 (1.37–2.96)	<0.001	1.17 (0.67–2.05)	0.58
Heart rate <60 beat/min	1.07 (0.79–0.79)	0.66	1.03 (0.72–1.49)	0.87
Body temperature ≥37.5 ºC	2.26 (1.72–2.7)	<0.001	1.89 (1.35–2.63)	<0.001
NYHA class III or IV	2.17 (1.62–2.91)	<0.001	1.69 (1.21–2.35)	0.002

*Defined by the World Health Organization criteria (haemoglobin <12 g/dL for women and <13 g/dL for men).

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; LVEF, left ventricular ejection; HF, heart failure; eGFR, estimated glomerular filtration rate; BP, blood pressure; NYHA, New York Heart Association.

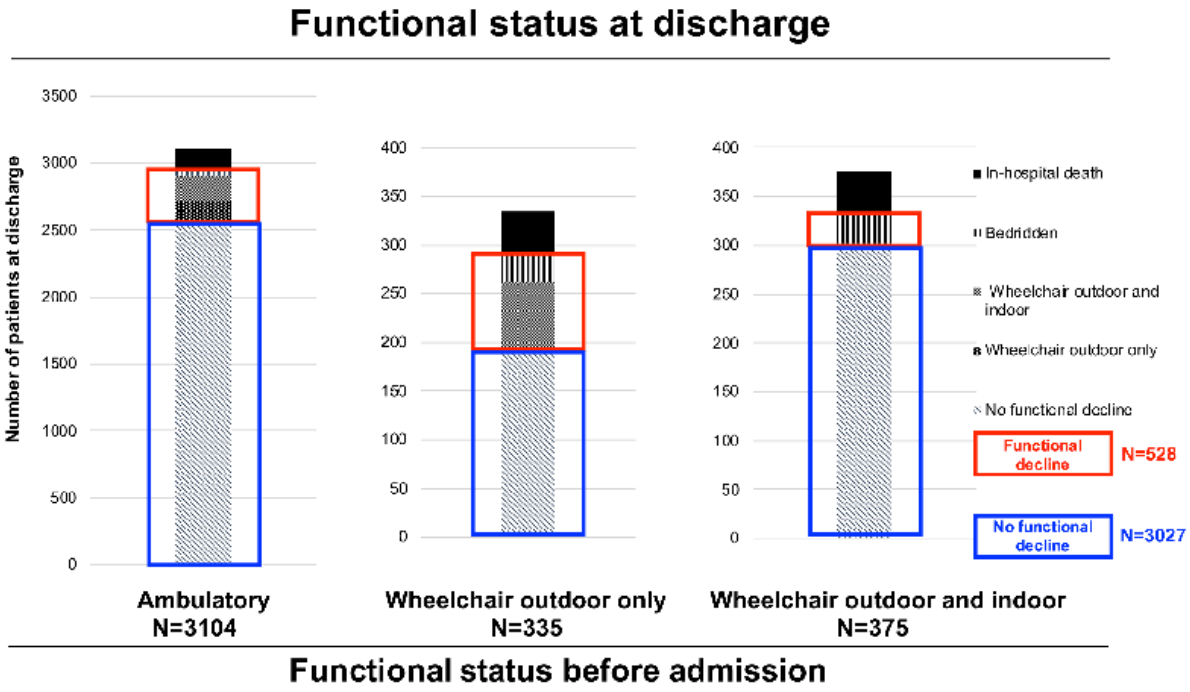
eTable 3. Clinical outcomes in the entire cohort

Outcomes	Functional decline	No functional decline	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
	N of patients with event / N of patients at risk (Cumulative 1-year incidence [%])	N of patients with event / N of patients at risk (Cumulative 1-year incidence [%])				
All-cause death or HF hospitalization	243/528 (49)	902/3027 (31)	1.95 (1.71–2.21)	<0.001	1.39 (1.18–1.62)	<0.001
All-cause death	174/528 (36)	386/3027 (13)	3.02 (2.58–3.53)	<0.001	1.92 (1.57–2.34)	<0.001
HF hospitalization	116/528 (28)	663/3027 (23)	1.25 (1.04–1.50)	0.02	0.99 (0.80–1.24)	0.97
All-cause death or All-cause hospitalization	279/528 (57)	1186/3027 (40)	1.69 (1.50–1.91)	<0.001	1.34 (1.15–1.55)	<0.001

The number of patients with at least one event was counted through the 1-year follow-up period.

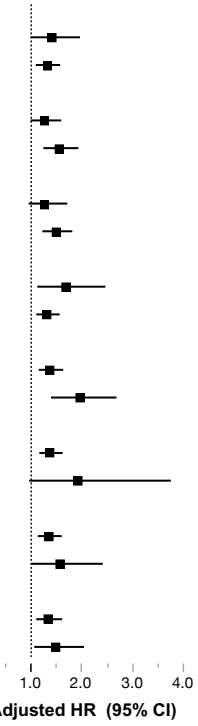
Abbreviations: HF, heart failure; HR, hazard ratio; CI, confidence interval.

eFigure 1. The details of functional decline during ADHF hospitalization. Functional status at discharge according to functional status before admission is shown. ADHF=acute decompensated heart failure.



eFigure 2. Subgroup analysis for the association of functional decline with no functional decline on the primary outcome measure. LVEF=left ventricular ejection fraction, HR=hazard ratio, CI=confidence interval.

	Functional decline	No functional decline	Adjusted HR (95% CI)	P value for interaction
	No. Events/No. at risk	No. Events/No. at risk		
Age, years				
<80	58/129	375/1620	1.40 (1.00–1.97)	0.65
≥80	185/399	527/1407	1.32 (1.10–1.58)	
Sex				
Female	122/294	383/1278	1.27 (1.00–1.60)	0.11
Male	121/234	519/1749	1.55 (1.25–1.94)	
LVEF, %				
<40	75/167	371/1148	1.29 (0.96–1.72)	0.20
≥40	168/359	528/1871	1.50 (1.23–1.82)	
Anaemia				
No	47/127	210/1075	1.67 (1.13–2.47)	0.11
Yes	196/401	691/1946	1.32 (1.11–1.57)	
Albumin <3.0 g/dL				
No	169/406	760/2605	1.38 (1.16–1.64)	0.14
Yes	67/112	117/332	1.95 (1.40–2.69)	
Body temperature ≥37.5 ºC				
No	211/447	815/2729	1.38 (1.17–1.63)	0.76
Yes	25/58	42/154	1.93 (0.97–3.76)	
Oedema at discharge				
No	184/423	739/2617	1.35 (1.14–1.61)	0.40
Yes	51/89	128/320	1.57 (1.01–2.42)	
General malaise at discharge				
No	142/331	690/2411	1.34 (1.11–1.62)	0.55
Yes	83/152	151/388	1.48 (1.07–2.05)	



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8
Bias	9	Describe any efforts to address potential sources of bias	Page 10
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	Page 10-11
		(*c*) Explain how missing data were addressed	Page 9
		(*d*) If applicable, explain how loss to follow-up was addressed	Page
		(*e*) Describe any sensitivity analyses	Page 11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	Page 8
		(c) Consider use of a flow diagram	Page 7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	Page 7-8
		(c) Summarise follow-up time (eg, average and total amount)	Page 12
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13-15
		(*b*) Report category boundaries when continuous variables were categorized	Page 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Risk factors and clinical outcomes of functional decline during hospitalization in very old patients with acute decompensated heart failure: an observational study

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Risk factors and clinical outcomes of functional decline during hospitalization in very old patients with acute decompensated heart failure: an observational study

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Abstract

Objective: To investigate the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in very old patients with acute decompensated heart failure (ADHF) hospitalization.

Design: Prospective cohort study between October 1, 2014, and March 31, 2016.

Setting: A physician-initiated multicentre study of consecutive patients admitted for ADHF into 19 hospitals throughout Japan.

Participants: Among 3555 patients hospitalized for ADHF (median age [IQR], 80 [71-86] years; 1572 [44%] women), functional decline during the index hospitalization occurred in 528 patients (15%).

Primary and secondary outcomes: The primary outcome measure was a composite of all-cause death or heart failure (HF) hospitalization after discharge. The secondary outcome measures were all-cause death, HF hospitalization, and a composite of all-cause death or all-cause hospitalization.

Results: The independent risk factors for functional decline included age ≥80 years (OR 2.71; 95%CI 2.09–3.51), women (OR 1.32; 95%CI 1.05–1.67), prior stroke (OR 1.67; 95% CI 1.28–2.19), dementia (OR 2.26; 95%CI 1.74–2.95), ambulatory before admission (OR

1.74; 95%CI 1.29–2.35), elevated body temperature (OR 1.91; 95%CI 1.31–2.79), New York Heart Association class III or IV on admission (OR 1.54; 95%CI 1.07–2.22), decreased albumin levels (OR 1.76; 95%CI 1.32–2.34), hyponatremia (OR 1.49; 95%CI 1.10–2.03), renal dysfunction (OR 1.55; 95%CI 1.22–1.98) after multivariable adjustment. The cumulative 1-year incidence of the primary outcome in the functional decline group was significantly higher than that in the no functional decline group (50% vs. 31%, log-rank P<0.001). After adjusting for baseline characteristics, the higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR 1.46; 95% CI 1.24–1.71; P<0.001).

Conclusions: Independent risk factors of functional decline in very old patients with ADHF were related to both frailty and severity of HF. Functional decline during ADHF hospitalization was associated with unfavourable post-discharge outcomes.

Trial Registration: https://clinicaltrials.gov/ct2/show/NCT02334891 (NCT02334891) and https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000017241 (UMIN000015238)

Strengths and limitations of this study

- This study is the first large-scale contemporary multicentre observational study reporting the prevalence of functional decline in very old patients hospitalized for acute decompensated heart failure (ADHF).
- The data of this study were prospectively collected on consecutive patients who had hospital admission due to ADHF in the real-world clinical practice in Japan.
- This study examines the risk factors of functional decline in very old patients hospitalized for ADHF, and whether functional decline during the index hospitalization was associated with worse post-discharge outcomes.
- We did not collect data regarding on-site and outpatient rehabilitation and nutritional support.

Introduction

Functional decline in hospitalized patients is a complex and dynamic process [1–3]. Functional decline during hospitalization was reported to occur in approximately 30-50% of patients hospitalized for acute medical illness [2,4,5]. In the rapidly aging societies, the number of very old patients hospitalized for acute decompensated heart failure (ADHF) is increasing, and ADHF has become the leading cause of hospitalization due to acute medical illness. In older patients, functional decline associated with hospitalization often leads to subsequent inability to live actively and independently.

However, there is a scarcity of data regarding the risk factors of functional decline in very old patients hospitalized for ADHF. Identifying high-risk patients for functional decline during hospitalization would be useful for its prevention. Furthermore, no previous study focused on subsequent clinical outcomes in patients with functional decline during hospitalization. Therefore, we sought to clarify the risk factors for functional decline during hospitalization in very old patients with ADHF and to compare the 1-year clinical outcomes between the 2 groups of patients with and without functional decline during the hospitalization for ADHF in a large Japanese observational database of hospitalized patients for ADHF in the real-world clinical practice.

Methods

Study Design, Setting, and Population

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled consecutive patients who were hospitalized for ADHF for the first time between October 1, 2014, and March 31, 2016. These patients were admitted into 19 secondary and tertiary hospitals, including rural and urban as well as large and small institutions, throughout Japan. The study protocol was approved by the institutional review board of Kyoto University (approval number: E2311) and each participating centre. A waiver of written informed consent from each patient was granted by the institutional review boards of Kyoto University and each participating centre because the study met the conditions of the Japanese ethical guidelines for epidemiological study and the US policy for protecting human research participants.[6,7] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The details of the KCHF study design and patient enrolment are described elsewhere.[8–11] Briefly, we enrolled all patients with ADHF, as defined by the modified Framingham criteria, who were admitted to the participating hospitals and patients who

underwent heart failure–specific treatment involving intravenous drugs within 24 hours after hospital presentation. Patient records were anonymized before analysis. Data analysis was conducted from August 2018 to October 2018.

Among 4056 patients enrolled in the KCHF registry, 3785 patients were discharged alive after hospitalization for ADHF. Clinical follow-up data were collected in October 2017. The attending physicians or research assistants at each participating hospital collected clinical events after the index hospitalization from hospital charts or by contacting patients, their relatives, or their referring physicians with consent. The present analysis had 2 objectives. First, we sought to clarify the risk factors for functional decline during hospitalization of ADHF patients. Second, we sought to compare the 1-year clinical outcomes between the 2 groups of patients with and without functional decline during the hospitalization for ADHF. Among 4056 patients enrolled in the KCHF registry, the current study population consisted of 3555 patients who were discharged alive and were assessed for functional decline during hospitalization, excluding 271 patients who died during the index hospitalization, 99 patients whose functional status before admission and/or at discharge was not available, and 131 patients who were bedridden before index hospitalization (Figure 1). The long-term follow-up was censored at 1-year. The primary outcome measure in the current analysis was a

composite of all-cause death or heart failure hospitalization at 1-year. The secondary outcome measures were all-cause death, heart failure hospitalization, and a composite of all-cause death or all-cause hospitalization at 1-year.

Definitions

Physical activity before admission and at discharge 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 stick), use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state.[8] Functional decline was defined as the decline of at least one stage on physical activity at discharge compared with pre-admission status. In-hospital worsening heart failure was defined as additional intravenous drug administration for heart failure, haemodialysis, or mechanical circulatory or respiratory support, occurring >24 hours after therapy initiation.[12] In-hospital worsening renal function was defined as >0.3 mg/dL increase in serum creatinine levels during the index hospitalization.[13–15] Detailed definitions of baseline clinical characteristics including the signs and symptoms of heart failure were described previously.[9] Missing values were presented in eTable 1.

Statistical Analysis

Categorical variables were presented as numbers with percentages and compared using χ^2 test. Continuous variables were expressed as the mean with standard deviation or median with 25th to 75th percentiles, and compared using the Student's *t* test when normally distributed or Wilcoxon rank-sum test when not normally distributed.

We compared baseline characteristics and clinical outcomes based on the presence or absence of functional decline during the index hospitalization. A multivariable logistic regression model was developed to identify clinical characteristics associated with an increased risk for functional decline. We used 24 clinically relevant factors listed in Table 1 as potential independent risk factors in multivariable logistic regression models and estimated the odd ratios (ORs) and 95% confidence intervals (CIs). We used the Kaplan-Meier method to estimate the cumulative 1-year incidences of the outcome measures and assessed the differences with the log-rank test. We expressed the associations of the functional decline group with the no functional decline group for all outcome measures as hazard ratios (HRs) with 95% CIs by multivariable Cox proportional hazard models incorporating 30 clinically relevant risk-adjusting variables indicated in Table 1. We also conducted subgroup analyses stratified by age, sex, LVEF, anaemia, albumin levels, body temperature, and the symptomatic status at discharge (oedema and general malaise at discharge). In the

multivariable analysis and subgroup analyses, continuous variables were dichotomized by clinically meaningful reference values or median values; age ≥80 years based on the median value, LVEF <40% based on the heart failure guideline of LVEF classification [16], BMI ≤22 kg/m^2, renal dysfunction (eGFR <30 ml/min/1.73m^2) based on CKD grade, decreased albumin levels (serum albumin <3.0 g/dL), hyponatremia (serum sodium <135 mEq/L), elevated body temperature (body temperature ≥37.5℃) based on the cut-off value in metabolic syndrome [17].

We performed an additional analysis using the data including those patients who died during the index hospitalization and those who were bedridden before the index hospitalization, and evaluated the factors associated with functional decline or in-hospital mortality by constructing the multivariable adjusted Cox models. All statistical analyses were conducted by a physician (H.Y.) and a statistician (T.M.) with JMP 13.0 or SAS 9.4 (both SAS Institute Inc, Cary, NC). Two-tailed P-values less than 0.05 were considered statistically significant.

Patient and public involvement

No patient involved.

Results

Baseline Clinical Characteristics

Among 3555 study patients, physical activity before admission included ambulatory in 2949 patients (83%), wheelchair outdoor only in 272 patients (7.7%), and wheelchair outdoor and indoor in 334 patients (9.4%). At hospital discharge, functional decline was observed in 420 patients (14%) who were ambulatory before admission, in 80 patients (29%) who had used wheelchair outdoor only, and in 28 patients (8.4%) who had used wheelchair outdoor and indoor. Consequently, decline in functional status was observed in 528 patients (15%; functional decline group), while functional decline was not observed in 3027 patients (85%; no functional decline group) (eFigure 1). Wheelchair outdoor only before admission were more prevalent in the functional decline group than in the no functional decline group; however, 80% of patients in the functional decline group were ambulatory before admission (Table 1).

Regarding the baseline clinical characteristics, the patients in the functional decline group were older and had a higher prevalence of hypertension, prior stroke, renal dysfunction, dementia, malignancy, anaemia, decreased albumin levels, and hyponatremia (Table 1). There were no significant differences in previous heart failure hospitalization,

atrial fibrillation or flutter, previous myocardial infarction, chronic lung disease, and living alone status as a social background between the 2 groups (Table 1). The functional decline group was more likely to have a valvular aetiology, lower blood pressure, lower heart rate, higher levels of brain natriuretic peptide (BNP) or N-terminal portion of proBNP (NT-proBNP), and a higher LVEF (Table 1). The proportion of patients who achieved relief of signs and symptoms on admission after the treatment in the emergency room was not significantly different between the 2 groups (14% vs. 16%, P=0.25).

Risk Factors for Functional Decline

Among the baseline characteristics and status at hospital presentation, the following independent risk factors for functional decline during hospitalization were identified by the multivariable logistic regression analysis: age ≥80 years (OR 2.71; 95% CI 2.09–3.51), women (OR 1.32; 95% CI 1.05–1.67), prior stroke (OR 1.67; 95% CI 1.28–2.19), dementia (OR 2.26; 95% CI 1.74–2.95), ambulatory before admission (OR 1.74; 95% CI 1.29–2.35), elevated body temperature (OR 1.91; 95% CI 1.31–2.79), New York Heart Association class III or IV on admission (OR 1.54; 95% CI 1.07–2.22), decreased albumin levels (OR 1.76; 95% CI 1.32–2.34), hyponatremia (OR 1.49; 95% CI 1.10–2.03), renal dysfunction (OR 1.55; 95% CI 1.22–1.98) (Figure 2).

In-hospital adverse events and status at discharge

The median length of hospital stay was longer in the functional decline group than in the no functional decline group (21 days vs. 15 days, P <0.001). Regarding the in-hospital adverse events, the prevalence of worsening heart failure, worsening renal function, and stroke was higher in the functional decline group than in the no functional decline group (Table 2). The proportion of patients with symptoms such as oedema and general malaise at discharge was higher in the functional decline group than in the no functional decline group (Table 1). Consequently, the proportion of patients in the functional decline group discharged to home was also lower (47% vs. 90%, P <0.001). Regarding medical treatment at discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI or ARB), and beta blocker were less often prescribed in the functional decline group than in the no functional decline group (Table 1).

Long-term outcomes: functional decline vs. no functional decline groups

Follow-up rate at 1-year was 96%. The cumulative 1-year incidence of the primary outcome measure (a composite of all-cause death or heart failure hospitalization) in the functional decline group was significantly higher than that in the no functional decline group (49% vs. 31%, log-rank P<0.001) (Figure 3). After adjusting for baseline characteristics, the

higher risk of the functional decline group relative to the no functional decline group remained significant (adjusted HR, 1.46; 95%CI, 1.24–1.71; P<0.001) (Figure 3 and Table 3). The cumulative 1-year incidence of all-cause death was also significantly higher in the functional decline group than in the no functional decline group. Even after adjusting confounders, the excess mortality risk of the functional decline group relative to the no functional decline group remained significant (Figure 3 and Table 3). The cumulative 1-year incidence of heart failure hospitalization was also significantly higher in the functional decline group than in the no functional decline group. However, the adjusted risk of the functional decline group relative to the no functional decline group for heart failure hospitalization was no longer significant (Figure 3 and Table 3). The cumulative 1-year incidence of a composite of all-cause death or all-cause hospitalization was significantly higher in the functional decline group than in the no functional decline group. After adjusting confounders, the higher risk of the functional decline group relative to the no functional decline group remained significant (Figure 3 and Table 3). In the subgroup analyses, there were no interactions between those subgroup factors and the association of functional decline with the primary outcome measure (eFigure 2).

Additional analysis on the risk factors for functional decline or in-hospital mortality

The risk factors for functional decline or in-hospital mortality in a total of 4056 patients were similar to the risk factors for functional decline. LVEF <40% (OR, 1.24; 95% CI, 1.00–1.52; P = 0.047) and acute coronary syndrome (OR, 1.76; 95% CI, 1.19–2.60; P = 0.005) that were not included in the risk factors for functional decline emerged as the risk factors for functional decline or in-hospital mortality (eTable 2). Meanwhile, among the risk factors for functional decline, women (OR, 1.13; 95% CI, 0.93–1.38; P = 0.22) was not included in the risk factors for functional decline or in-hospital mortality (Figure 2 and eTable 2).

Discussion

The main findings of the present study investigating the prevalence and risk factors of functional decline during hospitalization, and its relationship with post-discharge outcomes in patients with ADHF hospitalization were as follows; 1) Functional decline during ADHF hospitalization occurred in 15% of patients, and 80% of those with functional decline were ambulatory before admission; 2) The independent baseline risk factors associated with functional decline included age ≥80 years, women, prior stroke, dementia, ambulatory before admission, elevated body temperature, NYHA class III or IV on admission, decreased

albumin levels, hyponatremia, and renal dysfunction. 3) Functional decline during the index hospitalization was associated with higher long-term risk for a composite of all-cause death or heart failure hospitalization.

This is the first large-scale contemporary multicentre study reporting the prevalence of functional decline in patients hospitalized for ADHF. Of note, we identified the severity of symptoms or patient status specific for heart failure was associated with functional decline independent of well-known factors in acute medical illness [18–20]. Functional decline is an inevitable consequence in aged people, but hospitalization accelerates the decline [20–22]. Functional declines have been found to be related not only to impairment of independence and quality of life (QOL), but also to increased health service use, higher risk for institutionalization, and higher risk for mortality [23–27]. Indeed, in the present study, the proportion of patients discharged to home was lower in the functional decline group than in the no functional decline group, suggesting impaired QOL after discharge. Also, the long-term mortality was worse in the functional decline group than in the no functional decline group. Therefore, it is important to recognize risk factors of functional decline. In previous studies of hospitalized patients with acute medical illness, the predictors of functional decline in hospitalized elderly patients were older age, admission diagnosis, lower functional status,

impaired cognitive status, comorbidities, and length of hospital stay.[18–20] These findings were confirmed in the setting of ADHF in our present study. In addition, findings specific for ADHF such as the dyspnoea or hyponatremia was associated with functional decline, which were also reported to be the risk factors for in-hospital mortality in ADHF [28]. The prevalence of oedema and general malaise at discharge was higher in the functional decline group. Early achievement of successful ADHF treatment might reduce the risk of functional decline, although the present observational study could not address the cause-effect relationship between the functional decline and the symptomatic status at discharge.

There might be several possible strategies to prevent functional decline during ADHF hospitalization. The first is the early improvement of hemodynamic status to avoid worsening heart failure. The prevalence of worsening heart failure was higher in the functional decline group. As functional decline associated with hospitalization begins within 48 hours of admission, early improvement of heart failure to reduce the incidence of hospitalization-associated disability is one of the main goals of care.[28] Second, it would be important to be adequately aware high-risk patients to make aggressive intervention for preventing functional decline. We identified the risk factors among the baseline characteristics in ADHF patients. In addition, the adverse events during hospitalization may

be tightly related to the functional decline. Stroke is one of causes of functional decline and observed in 5.1% of patients with functional decline. Third, a strategy for the prevention of functional decline might be the seamless rehabilitation and comprehensive geriatric management through a multidisciplinary team approach.[29–32] In addition, the subgroup analysis showed that there were no interactions between those subgroup factors and the association of functional decline with the primary outcome measure. Thus, prevention of functional decline would have an impact on improving outcomes in all of the patients with ADHF. One possible strategy could be immediate, tailored physical function rehabilitation during and after heart failure hospitalization.[33]

Limitations

This study has several limitations. First, we adopted simple classification of functional status as ambulatory, use of wheelchair outdoor only, use of wheelchair indoor and outdoor, and bedridden state based on the definition of Japanese long-term care insurance. The categorization scheme is an easy to understand but coarse measure with very large gradations inherent in each single stage and therefore very likely substantially underestimated the prevalence of meaningful functional decline. Second, we did not collect data regarding on-site and outpatient rehabilitation and nutritional support. However, a team-based approach

for heart failure patients was adapted in all the participating centres in the present study. Third, we did not include the status at discharge or adverse in-hospital events in the analysis for the risk factor for functional decline, because the cause-effect relationship was not clear. Fourth, data on post-discharge medication and change of functional status after discharge from the index hospitalization were not collected, and not analysed in the analysis for the long-term outcomes. Fifth, as with any observational study, the possibility of selection bias and residual confounding cannot be excluded, although we adjusted for 29 variables as most conceivable confounders.

Conclusions

Independent risk factors of functional decline in ADHF patients were related to both frailty and severity of heart failure. Functional decline during ADHF hospitalization was associated with unfavourable post-discharge outcomes.

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Competing interests

None declared.

Author Contributions

Drs Yaku and T. Kato had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yaku, T. Kato, Morimoto, Tamaki, Ozasa, Yamamoto, Kitai, M. Kato, Kimura.

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Statistical analysis: Yaku, T. Kato, Morimoto.

Administrative, technical, or material support: T. Kato, Sato, Kimura.

Supervision: Inuzuka, Ozasa, Kitai, Furukawa, Nakagawa, Sato, Kuwahara, Kimura.

Ethics approval

The study was approved by the Institutional Review Boards of Kyoto University Graduate School of Medicine (approval number: E2311), Shiga General Hospital (approval number: 20141120-01), Tenri Hospital (approval number: 640), Kobe City Medical Centre General Hospital (approval number: 14094), Hyogo Prefectural Amagasaki General Medical Centre

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Data sharing

All data relevant to the study are included in the article or uploaded as supplementary information. No additional data available.

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Figure legends

Figure 1. **Patient flowchart.** KCHF, Kyoto Congestive Heart Failure; ADHF, acute decompensated heart failure.

Figure 2. Clinical factors associated with functional decline during hospitalization in the univariate and multivariable logistic regression models. OR, odds ratio; CI, confidence interval; BMI, body mass index; HF, heart failure; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection; eGFR, estimated glomerular filtration rate.

Figure 3. **The Cumulative incidences for the primary outcome measure (A), for all-cause death (B), for HF hospitalization (C), and for a composite of all-cause death or all-cause hospitalization (D) according to the presence or absence of functional decline.**

HF=heart failure, HR=hazard ratio, CI=confidence interval.

Table 1. Patient Characteristics

	Functional decline	No functional decline	P value
	N=528	N=3027	
Clinical characteristics			
Age, years	85 [80–89]	79 [70–85]	<0.001
Age ≥80 years*†	399 (76)	1407 (46)	<0.001
Women*†	294 (56)	1278 (42)	<0.001
BMI, kg/m^2	22.0±4.0	23.1±4.5	<0.001
BMI ≤22 kg/m^2*†	269 (55)	1281 (44)	<0.001
Medical history			
Prior heart failure hospitalization*†	186 (36)	1077 (36)	0.92
Atrial fibrillation or flutter	220 (42)	1263 (42)	0.98
Hypertension*†	406 (77)	2174 (72)	0.02
Diabetes mellitus*†	187 (35)	1145 (38)	0.29
Prior myocardial infarction*†	112 (21)	681 (23)	0.51
Prior stroke*†	125 (24)	432 (14)	<0.001
Current smoking*†	28 (5.5)	425 (14)	<0.001
Malignancy	97 (18)	419 (14)	0.006
Chronic lung disease*†	41 (7.8)	247 (8.2)	0.76
Dementia*†	175 (33)	423 (14)	<0.001
Social backgrounds at admission			
Poor medical adherence	100 (19)	498 (16)	0.16
Living alone*†	127 (24)	652 (22)	0.20
Public assistance	24 (4.6)	186 (6.1)	0.14
Functional status before admission			
Ambulatory*†	420 (80)	2529 (84)	0.02
Use of wheelchair [outdoor only]	80 (15)	192 (6.3)	<0.001
Use of wheelchair [outdoor and indoor]	28 (5.3)	306 (10)	<0.001
Origin			
Ischemic	134 (25)	820 (27)	0.41
Acute coronary syndrome*†	36 (6.8)	166 (5.5)	0.22
Hypertensive	131 (25)	754 (25)	0.96
Valvular	124 (23)	565 (19)	<0.001

Cardiomyopathy	54 (10)	492 (16)	<0.001
Vital signs and symptoms at presentation			
BP, mmHg			
Systolic BP	144±32	149±35	0.003
Systolic BP ≥140 mmHg	275 (53)	1741 (58)	0.03
Systolic BP <90 mmHg*†	12 (2.3)	76 (2.5)	0.76
Diastolic BP	81±23	86±24	<0.001
Heart rate, beat/min	93±27	96±28	0.001
Heart rate <60 beat/min*†	44 (8.5)	195 (6.5)	0.11
Body temperature, ºC	36.6±0.7	36.5±0.6	<0.001
Body temperature ≥37.5ºC*†	58 (11)	154 (5.3)	<0.001
Rhythms at presentation			
Sinus rhythm	280 (53)	1715 (57)	0.12
Atrial fibrillation or flutter*†	198 (38)	1085 (36)	0.47
NYHA class III or IV*†	482 (92)	2598 (73)	<0.001
Tests at admission			
LVEF	48±16	46±16	0.02
HFrEF (EF<40%)*†	167 (32)	1148 (38)	0.006
HFmrEF (EF 40–49%)	117 (22)	566 (19)	0.06
HFpEF (EF ≥50%)	242 (46)	1305 (43)	0.24
Haemoglobin, g/dL	11.0±2.1	11.7±2.4	<0.001
Anaemia*†‡	401 (76)	1946 (64)	<0.001
BNP, pg/ml	782 [448–1410]	687 [375–1214]	<0.001
NT-proBNP, pg/ml	10795 [3450–18000]	5416 [2629–11438]	0.001
Creatinine, mg/dL	1.2 [0.8–1.6]	1.1 [0.8–1.6]	0.21
eGFR, ml/min/1.73m^2	38 [24–54]	46 [30–62]	<0.001
eGFR <30 ml/min/1.73m^2*†	195 (37)	747 (25)	<0.001
Blood urea nitrogen, mg/dL	28 (20–39)	23 (17–33)	<0.001
Albumin, g/dL	3.3±0.5	3.5±0.5	<0.001
Albumin <3.0 g/dL*†	112 (22)	332 (11)	<0.001
Sodium, mEq/L	138±4.7	139±4.1	<0.001
Sodium <135 mEq/L*†	83 (16)	325 (11)	0.001
Potassium, mEq/L	4.3±0.8	4.2±0.6	0.03
Clinical signs and symptoms at discharge			

Oedema†	89 (17)	320 (11)	<0.001
General malaise†	152 (31)	388 (14)	<0.001
Medications at discharge			
Number of drugs prescribed	8 (6–11)	9 (6–11)	0.12
Loop diuretics†	428 (81)	2472 (82)	0.74
ACEI or ARB†	242 (46)	1838 (61)	<0.001
MRA†	208 (39)	1409 (47)	0.002
Beta blocker†	287 (54)	2101 (69)	<0.001
Tolvaptan	76 (14)	299 (9.9)	0.002
Functional status at discharge			
Ambulatory	0	2682 (89)	<0.001
Use of wheelchair [outdoor only]	184 (35)	160 (5.3)	<0.001
Use of wheelchair [outdoor and indoor]	261 (49)	185 (6.1)	<.0001
Bedridden	83 (16)	0	<0.001
Living place after discharge			
Home	247 (47)	2709 (90)	<0.001
Hospital	225 (43)	180 (6.0)	<0.001
Institution for the aged	50 (9.5)	114 (3.8)	<0.001
Other	4 (0.8)	17 (0.6)	0.59

Abbreviations: BMI, body mass index; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; BNP, brain-type natriuretic peptide; NT-proBNP, N-terminal-proBNP; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Continuous variables were presented as mean ± SD or median with [interquartile range]. Categorical variables were presented as number (percentage).

* Risk-adjusting variables were selected for multivariable logistic regression models.

† Risk-adjusting variables were selected for multivariable Cox proportional hazard models.

‡ Defined by the World Health Organization criteria (haemoglobin <12 g/dL for women and <13 g/dL for men).

1

Table 2. In-hospital Management and Outcome

	Functional decline	No functional decline	P value
	N=528	N=3027	
In-hospital management			
Management in the emergency room			
Respiratory management			
Oxygen inhalation	295 (56)	1382 (46)	<0.001
NIPPV	82 (16)	423 (14)	0.35
Intubation	11 (2.1)	53 (1.8)	0.60
Intravenous drugs within 24 hours after hospital presentation			
Inotropes	101 (19)	405 (13)	<0.001
Furosemide	446 (85)	2536 (84)	0.69
In-hospital clinical outcomes			
In-hospital adverse events			
Stroke	27 (5.1)	26 (0.9)	<0.001
Worsening heart failure	130 (25)	490 (16)	<0.001
Worsening renal function	244 (47)	992 (33)	<0.001
In-hospital infection	104 (20)	258 (8.5)	<0.001
Length of stay, day	21 [14–37]	15 [11–22]	<0.001

Abbreviations: NIPPV, non-invasive intermittent positive pressure ventilation.

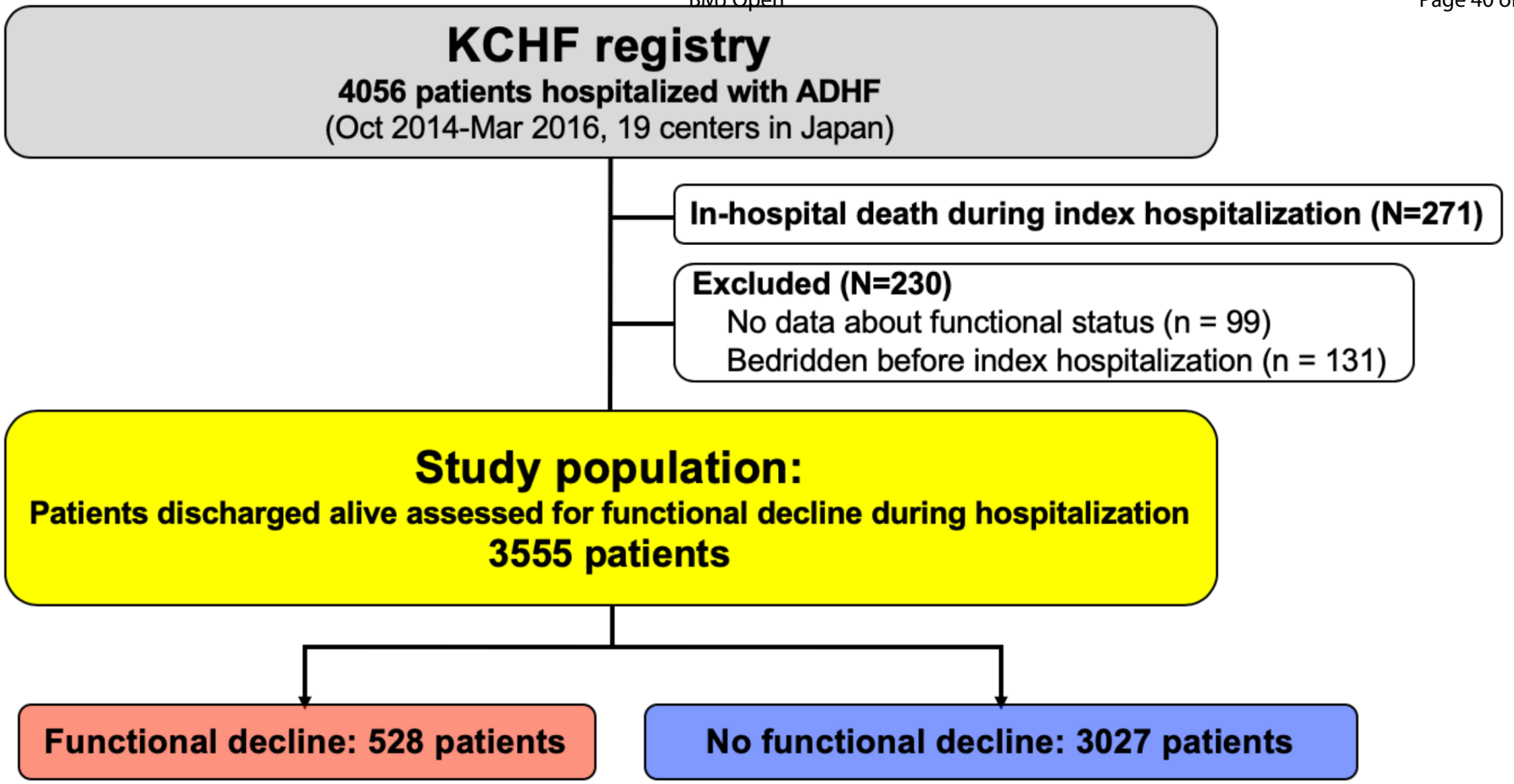
1

Table 3. Clinical outcomes in the entire cohort

Outcomes	Functional decline	No functional decline	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
	N of patients with event / N of patients at risk (Cumulative 1-year incidence [%])	N of patients with event / N of patients at risk (Cumulative 1-year incidence [%])				
All-cause death or HF hospitalization	243/528 (49)	902/3027 (31)	1.95 (1.71–2.21)	<0.001	1.46 (1.24–1.71)	<0.001
All-cause death	174/528 (36)	386/3027 (13)	3.02 (2.58–3.53)	<0.001	2.12 (1.74–2.58)	<0.001
HF hospitalization	116/528 (28)	663/3027 (23)	1.25 (1.04–1.50)	0.02	1.03 (0.83–1.28)	0.81
All-cause death or All-cause hospitalization	279/528 (57)	1186/3027 (40)	1.69 (1.50–1.91)	<0.001	1.39 (1.20–1.61)	<0.001

The number of patients with at least one event was counted through the 1-year follow-up period.

Abbreviations: HF, heart failure; HR, hazard ratio; CI, confidence interval.


KCHF registry
4056 patients hospitalized with ADHF
(Oct 2014-Mar 2016, 19 centers in Japan)
In-hospital death during index hospitalization (N=271)
Excluded (N=230)
No data about functional status (n = 99)
Bedridden before index hospitalization (n = 131)
Study population:
Patients discharged alive assessed for functional decline during hospitalization
3555 patients
Functional decline: 528 patients
No functional decline: 3027 patients

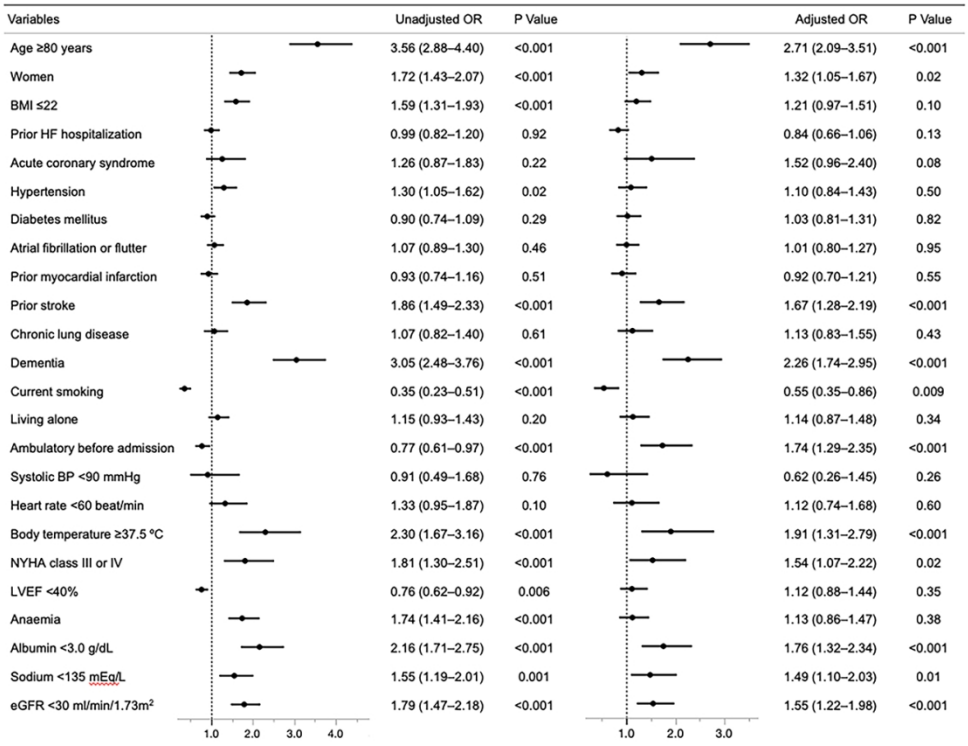


Figure 2. Clinical factors associated with functional decline during hospitalization in the univariate and multivariable logistic regression models.

Figure 3A

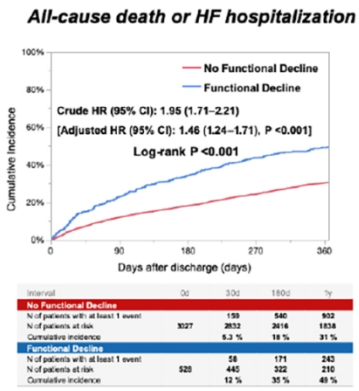


Figure 3B

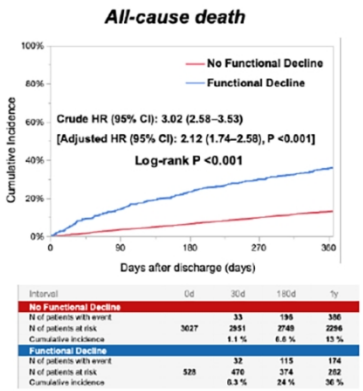


Figure 3C

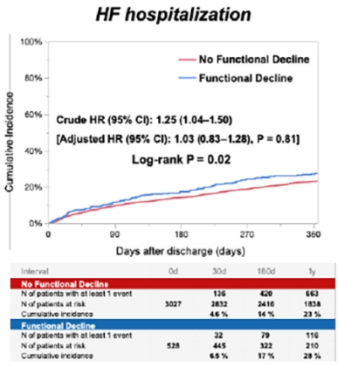


Figure 3D

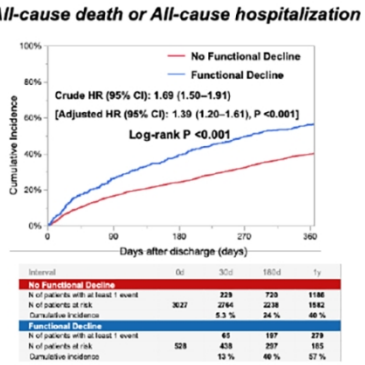


Figure 3. The Cumulative incidences for the primary outcome measure (A), for all-cause death (B), for HF hospitalization (C), and for a composite of all-cause death or all-cause hospitalization (D) according to the presence or absence of functional decline.

Supplementary Online Content

eTable 1. Number of missing values in in the entire cohort

eTable 2. Clinical factors associated with functional decline or in-hospital mortality in the univariate and multivariable analyses in a total of 4056 patients

eFigure 1. The details of functional decline during ADHF Hospitalization.

eFigure 2. Subgroup analysis for the association of functional decline with no functional decline on the primary outcome measure.

eTable 1. Number of missing values in the entire cohort

	Entire Cohort (N=3555)	
	Number	**Rate (%)**
Tests at admission		
BNP or NT-proBNP *	41	1.15
Serum creatinine	5	0.14
eGFR	5	0.14
Blood urea nitrogen	8	0.22
Albumin	100	2.81
Sodium	11	0.31
Potassium	11	0.31
Haemoglobin	6	0.17

* BNP values were reported for 3140 patients in the entire cohort; NT-proBNP values were reported for 633 patients in the entire cohort.

Abbreviation: BNP, brain-type natriuretic peptide; NT-proBNP, N-terminal-proBNP; eGFR, estimated glomerular filtration rate.

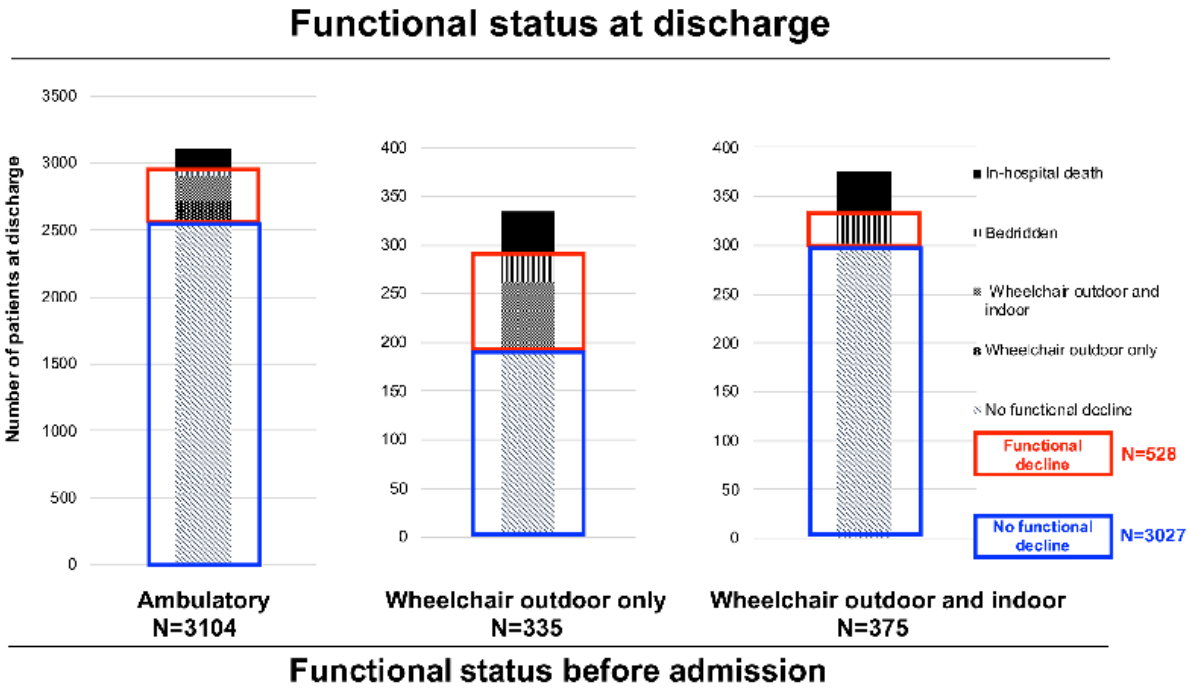
eTable 2. Clinical factors associated with functional decline or in-hospital mortality in the univariate and multivariable analyses in a total of 4056 patients

Variables	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age ≥80 years	2.97 (2.50–3.52)	<0.001	2.32 (1.86–2.89)	<0.001
Women	1.45 (1.25–1.70)	<0.001	1.13 (0.93–1.38)	0.22
BMI ≤22	1.56 (1.32–1.83)	<0.001	1.21 (1.00–1.47)	0.053
Prior HF hospitalization	1.08 (0.92–1.27)	0.36	0.96 (0.79–1.18)	0.72
Acute coronary syndrome	1.56 (1.16–2.11)	0.003	1.76 (1.19–2.60)	0.005
Hypertension	1.00 (0.85–1.20)	0.95	0.96 (0.77–1.21)	0.75
Diabetes mellitus	0.86 (0.73–1.01)	0.06	0.88 (0.72–1.09)	0.25
Atrial fibrillation or flutter	0.97 (0.83–1.13)	0.67	0.99 (0.81–1.21)	0.90
Prior myocardial infarction	0.94 (0.78–1.13)	0.50	0.89 (0.71–1.13)	0.36
Prior stroke	1.73 (1.43–2.10)	<0.001	1.57 (1.24–1.99)	<0.001
Chronic lung disease	1.11 (0.89–1.39)	0.37	1.16 (0.88–1.52)	0.29
Dementia	2.91 (2.44–3.47)	<0.001	2.24 (1.78–2.82)	<0.001
Current smoking	0.37 (0.27–0.51)	<0.001	0.55 (0.38–0.81)	0.002
Living alone	1.05 (0.87–1.27)	0.62	1.14 (0.91–1.44)	0.26
Ambulatory before admission	0.64 (0.54–0.77)	<0.001	1.44 (1.13–1.84)	0.003
Systolic BP <90 mmHg	2.01 (1.37–2.96)	<0.001	1.17 (0.66–2.05)	0.59
Heart rate <60 beat/min	1.07 (0.79–0.79)	0.66	1.03 (0.71–1.49)	0.88
Body temperature ≥37.5 ºC	2.26 (1.72–2.7)	<0.001	1.89 (1.35–2.63)	<0.001
NYHA class III or IV	2.17 (1.62–2.91)	<0.001	1.73 (1.24–2.41)	0.001
LVEF <40%	1.04 (0.89–1.22)	0.61	1.24 (1.00–1.52)	0.047
Anaemia*	1.67 (1.39–1.98)	<0.001	1.08 (0.86–1.36)	0.51
Albumin <3.0 g/dL	2.30 (1.89–2.81)	<0.001	1.91 (1.50–2.43)	<0.001
Sodium <135 mEq/L	1.89 (1.53–2.33)	<0.001	1.72 (1.34–2.22)	<0.001
eGFR <30 ml/min/1.73m^2	2.01 (1.70–2.36)	<0.001	1.78 (1.45–2.19)	<0.001

*Defined by the World Health Organization criteria (haemoglobin <12 g/dL for women and <13 g/dL for men).

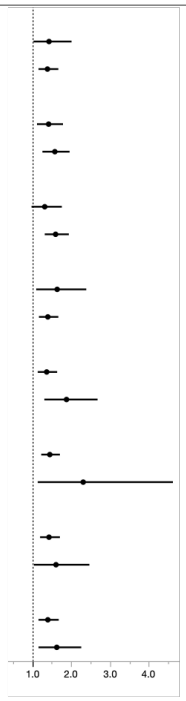
Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HF, heart failure; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection; eGFR, estimated glomerular filtration rate;.

eFigure 1. The details of functional decline during ADHF hospitalization. Functional status at discharge according to functional status before admission is shown. ADHF, acute decompensated heart failure.



eFigure 2. Subgroup analysis for the association of functional decline with no functional decline on the primary outcome measure. LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

	Functional decline	No functional decline	Adjusted HR (95% CI)	P value for interaction
	No. Events/No. at risk	No. Events/No. at risk		
Age, years				
<80	58/129	375/1620	1.43 (1.03–2.01)	0.70
≥80	185/399	527/1407	1.39 (1.16–1.67)	
Sex				
Female	122/294	383/1278	1.42 (1.12–1.79)	0.23
Male	121/234	519/1749	1.58 (1.26–1.96)	
LVEF, %				
<40	75/167	371/1148	1.32 (0.98–1.76)	0.17
≥40	168/359	528/1871	1.60 (1.32–1.94)	
Anaemia				
No	47/127	210/1075	1.64 (1.10–2.39)	0.16
Yes	196/401	691/1946	1.40 (1.17–1.67)	
Albumin <3.0 g/dL				
No	169/406	760/2605	1.37 (1.14–1.64)	0.16
Yes	67/112	117/332	1.88 (1.31–2.68)	
Body temperature ≥37.5 °C				
No	211/447	815/2729	1.45 (1.23–1.71)	0.74
Yes	25/58	42/154	2.31 (1.14–4.62)	
Oedema at discharge				
No	184/423	739/2617	1.43 (1.20–1.71)	0.42
Yes	51/89	128/320	1.61 (1.04–2.47)	
General malaise at discharge				
No	142/331	690/2411	1.40 (1.16–1.68)	0.31
Yes	83/152	151/388	1.63 (1.16–2.26)	



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			
Study design	4	Present key elements of study design early in the paper	Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8
Bias	9	Describe any efforts to address potential sources of bias	Page 10
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	Page 10-11
		(*c*) Explain how missing data were addressed	Page 9
		(*d*) If applicable, explain how loss to follow-up was addressed	Page
		(*e*) Describe any sensitivity analyses	Page 11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 12
		(b) Give reasons for non-participation at each stage	Page 8
		(c) Consider use of a flow diagram	Page 7-8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 12
		(b) Indicate number of participants with missing data for each variable of interest	Page 7-8
		(c) Summarise follow-up time (eg, average and total amount)	Page 12
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 13-15
		(*b*) Report category boundaries when continuous variables were categorized	Page 10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 14-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.