学位論文

Prevalence, determinants, and prognostic significance of delirium in patients with acute heart failure

（急性心不全におけるせん妄の頻度、規定因子と予後への影響）

本田　怜史
Satoshi Honda

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

指導教員

安田　聡　客員教授
熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

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中表紙

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著 者 名　：　本　田　怜　史
（単名）　Satoshi　Honda

指導教員名　：　熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学　安田　聡　客員教授

審査委員名　：　心臓血管外科学担当教授　氏　名　福井寿啓
救急・総合診療医学担当教授　氏　名　笠岡俊志
循環器内科学担当教授　氏　名　辻田賢一

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Prevalence, determinants, and prognostic significance of delirium in patients with acute heart failure

Satoshi Honda [a,b], Toshiyuki Nagai [a,*], Yasuo Sugano [a], Atsushi Okada [a], Yasuhide Asaumi [a], Takeshi Aiba [a], Teruo Noguchi [a], Kengo Kusano [a], Hisao Ogawa [a], Satoshi Yasuda [a,b], Toshihisa Anzai [a], On behalf of the NaDEF investigators

[a] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan
[b] Department of Advanced Cardiovascular Medicine, Graduated School of Medical Science, Kumamoto University, Kumamoto, Japan

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ABSTRACT

Background: Delirium is a serious syndrome in critically ill patients. However, the prognostic impact of delirium and its determinants in acute heart failure (AHF) patients have not been fully elucidated.
Methods: We examined 611 AHF patients who were admitted to our institution. Delirium was diagnosed based on the Intensive Care Delirium Screening Checklist (ICDSC).
Results: Delirium developed in 139 patients (23%) during hospitalization. Patients with delirium had higher incidence of non-cardiovascular death ($p = 0.046$) and worsening heart failure ($p < 0.001$) during hospitalization. Among patients who survived at discharge, the incidence of all-cause death, cardiovascular death and non-cardiovascular death after discharge were significantly higher in patients with delirium than those without (log-rank; $p < 0.001$, $p = 0.001$, $p < 0.001$, respectively) during a median follow-up period of 335 days. In multivariable model, the development of delirium was an independent determinant of worsening heart failure during hospitalization (OR: 2.44, 95% CI: 1.27–4.63) and all-cause death after discharge (HR: 2.38, 95% CI: 1.30–4.35). Furthermore, multivariate analysis indicated that history of cerebrovascular disease (OR: 2.13, 95% CI: 1.36–3.35), age (OR: 1.43, 95% CI: 1.15–1.80), log BNP (OR: 1.39, 95% CI: 1.09–1.79), serum albumin (OR: 0.84, 95% CI: 0.76–0.93) and blood glucose levels (OR: 1.03, 95% CI: 1.00–1.06) were independent determinants of delirium.
Conclusion: In patients with AHF, the development of delirium was associated with poor clinical outcomes, suggesting the importance of early screening and careful monitoring of delirium in such patients.

1. Introduction

Delirium is an acute confusional state characterized by disturbance of consciousness and a change in cognition that is commonly observed in hospitalized patients, particularly among those with older age and critical illness [1]. Several studies have demonstrated that the development of delirium during intensive care is associated with prolonged hospital stay and increased mortality in critically ill or postoperative patients [2–5].

Heart failure (HF) is a major growing public health problem worldwide, with high morbidity, mortality, and heavy economic burden [6]. Acute HF (AHF) is a severe medical condition that requires intensive medical support, and about 80% of patients with AHF are elderly and may be at high risk of development of delirium [7,8].

Although a few studies have demonstrated an association between the development of delirium and worse short-term clinical outcomes in hospitalized HF patients [9,10], its long-term prognostic implication and determinants in AHF patients have not been fully elucidated. In addition, although there is no evidence-based effective treatment protocol for delirium in patients with AHF, early identification of patients at high risk for delirium would be important for risk stratification and preventive management. Hence, the purpose of this study was first to investigate the incidence and prognostic significance of the development of delirium, and second to identify its practically useful predictors in patients with AHF.

2. Methods

2.1. Study design

Data from the NaDEF (National cerebral and cardiovascular center acute DEcompensated heart Failure) registry, which were obtained between January 2013 and March 2015, were retrospectively analyzed.

* Corresponding author at: Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan.
E-mail address: nagai@ncvc.go.jp (T. Nagai).

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The NaDEF registry is a single-center, observational, on-going, prospective cohort that includes all patients requiring hospitalization to our institution from January 2013 for the first time with a diagnosis of HF by at least two experienced cardiologists according to the Framingham criteria [11], and follow-up was performed at 3, 6, 12, and 24 months after discharge by direct contact with patients or their physicians in the hospital or outpatient clinic, telephone interview of patients or, if deceased, of family members, and mail, by dedicated coordinators and investigators. In this study, because patient information was anonymized and de-identified prior to analyses, written informed consent was not obtained from each patient. However, we publicized the study by posting a summary of the protocol (with an easily understood description) on the website of the National Cerebral and Cardiovascular Center; the notice clearly informed patients of their right to refuse enrollment. These procedures for informed consent and enrollment were in accordance with the detailed regulations regarding informed consent described in the guidelines, and this study, including the procedure for enrollment, has been approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center (M22-025), and registered under the Japanese UMIN Clinical Trials Registration (UMIN000017024).

2.2. Study population

A total of 651 consecutive patients with AHF were registered in the NaDEF registry. Patients with acute coronary syndrome (n = 34) and those without data regarding delirium (n = 6) were excluded. Finally, 611 patients were included in this study. Among them, 248 patients (44.8%) were admitted to a cardiovascular intensive care unit (CICU). Patients were divided into two groups according to the presence or absence of the development of delirium during hospitalization.

2.3. Definition of delirium

Screening for delirium was performed by a well-trained nurse at least 3 times a day. Delirium was diagnosed using the Intensive Care Delirium Screening Checklist (ICDSC). ICDSC is a well-validated tool that is recommended as a screening tool for delirium in the guidelines for Pain, Agitation, and Delirium (PAD) [12]. Patients were considered to have delirium when they had a score of 4 out of 8 points or higher in the ICDSC. A cut-off score of 4 has a sensitivity of 99% and a specificity of 64% for identifying delirium in patients admitted to intensive care units [13].

2.4. Study endpoints

Clinical outcomes that developed during hospitalization and after discharge were assessed separately to evaluate the impact of delirium on short- and long-term clinical outcomes. The primary in-hospital adverse events were all-cause death and worsening HF, which was defined as worsening symptoms and signs of HF requiring intensification of intravenous therapy or initiation of mechanical support after stabilization with initial treatment during hospitalization [14,15]. The secondary in-hospital adverse events were cardiovascular death, non-cardiovascular death and length of hospital stay. The primary adverse events after discharge were all-cause death and readmission for worsening HF. The secondary adverse events after discharge were cardiovascular death and non-cardiovascular death.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range: IQR). Normally distributed continuous variables were compared using unpaired *t* test. Non-normally distributed continuous variables were compared using the Kruskal–Wallis test. Categorical variables are shown as frequencies with percentages and were compared between the two groups using chi-squared test. Multivariate logistic regression analysis, which included variables with a p value ≤0.05 in the univariate analysis, was used to assess the determinants of worsening HF during hospitalization. Survival and event-free survival after discharge were estimated using Kaplan–Meier curves, and log-rank (Mantel–Cox) test was used to assess differences according to the presence or absence of the development of delirium during hospitalization. Multivariate Cox proportional hazard model analysis, which included variables with a p value ≤0.05 in the univariate analysis, was used to assess the association of these factors with all-cause death after discharge. Multivariate logistic regression analysis, which included determinants with a p value ≤0.05 in the univariate analysis, was performed to assess the determinants of the development of delirium in patients with AHF. All analyses were performed using the statistical software JMP® 10.0.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a p value <0.05.

3. Results

3.1. Patient characteristics

During hospitalization, 139 of 611 patients (23%) experienced delirium. The incidence of delirium was significantly higher in patients admitted to CICU than those without (28.5% vs. 18.3%, p = 0.003). The baseline characteristics on admission are shown in Tables 1 and 2. Patients with delirium were older and had a higher prevalence of cerebrovascular disease (CVD), higher brain natriuretic peptide (BNP), higher serum glucose, dopamine, norepinephrine and epinephrine levels, and lower body mass index (BMI), serum albumin level and estimated glomerular filtration rate (eGFR) than those without. There were no significant differences between the groups in terms of gender, etiology of HF, prevalence of New York Heart Association (NYHA) class III or IV, history of HF admission, previous history of depression, malignancy, chronic kidney disease (CKD), systolic blood pressure (BP), left ventricular ejection fraction (LVEF), total bilirubin, hemoglobin and HbA1c levels and medications on admission.

3.2. In-hospital treatment and outcomes

Treatment during hospitalization is summarized in Table 3. The prevalence of CICU admission was significantly higher in patients with

Table 1
Baseline characteristics of patients.

Variable	Overall (n = 611)	Delirium (n = 139)	No delirium (n = 472)	p value
Age, year	75.2 ± 12.3	79.5 ± 11.5	73.9 ± 12.2	<0.001
Female, n (%)	238 (39.0)	59 (42.5)	179 (37.9)	0.34
NYHA class III or IV, n (%)	505 (88.8)	118 (90.8)	387 (88.2)	0.40
BMI, kg/m^2	23.0 ± 4.2	22.1 ± 3.9	23.2 ± 4.2	0.011
Ischemic etiology, n (%)	141 (23.1)	31 (22.3)	110 (23.3)	0.81
LVEF, %	38.0 ± 17.1	39.2 ± 17.0	37.7 ± 17.1	0.41
Past history, n (%)				
Hypertension	428 (70.3)	101 (73.2)	327 (69.4)	0.40
Diabetes	217 (35.8)	52 (37.7)	165 (35.2)	0.59
HF admission	286 (46.9)	66 (47.8)	220 (46.6)	0.80
Atrial arrhythmia	318 (52.1)	68 (49.3)	250 (53.0)	0.45
Cerebrovascular disease	157 (25.8)	53 (38.4)	104 (22.1)	0.001
Malignancy	92 (15.2)	28 (20.3)	64 (13.7)	0.057
CKD	344 (56.6)	85 (61.1)	259 (55.2)	0.22
COPD	25 (4.1)	6 (4.4)	19 (4.0)	0.87
Depression	18 (2.9)	6 (4.4)	12 (2.6)	0.26
Current smoking, n (%)	69 (21.1)	17 (22.4)	52 (20.7)	0.76
Habitual drinking, n (%)	132 (47.1)	28 (50.9)	104 (46.2)	0.53
Systolic BP, mm Hg	138.7 ± 32.2	137.9 ± 34.4	138.9 ± 31.5	0.75
Heart rate, beat/min	91.9 ± 28.6	92.2 ± 28.7	91.8 ± 28.6	0.88

Values are mean ± standard deviation or percentages. NYHA = New York Heart Association; BMI = body mass index; LVEF = left ventricular ejection fraction; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; BP = blood pressure.

Table 2
Laboratory data and medications on admission.

Variable	Overall (n = 611)	Delirium (n = 139)	No delirium (n = 472)	p value
Laboratory data				
Serum albumin, g/dL	3.7 ± 0.4	3.6 ± 0.5	3.8 ± 0.4	<0.001
Total bilirubin, mg/dL	0.7 (0.5–1.1)	0.8 (0.5–1.1)	0.7 (0.5–1.0)	0.60
Sodium, mEq/L	139.5 ± 4.4	138.9 ± 4.8	139.7 ± 4.2	0.041
BNP, pg/mL	593 (311–1119)	736 (423–1371)	552 (274–1065)	0.004
eGFR, mL/min/1.73 m^2	45.8 ± 22.1	40.8 ± 22.5	47.3 ± 21.8	0.002
Hemoglobin, g/dL	11.9 ± 2.1	11.7 ± 2.1	12.0 ± 2.1	0.101
CRP, mg/dL	0.4 (0.1–1.4)	0.4 (0.1–2.2)	0.4 (0.1–1.2)	0.32
Blood glucose, mg/dL	146.3 ± 62.2	162.0 ± 80.1	141.7 ± 55.1	0.001
HbA1c, %	6.1 ± 0.9	6.2 ± 1.0	6.1 ± 0.9	0.34
Dopamine, pg/mL	23.0 (16.0–39.0)	27.0 (19.5–62.0)	22.5 (15.0–35.0)	<0.001
Norepinephrine, pg/mL	611 (392–887)	713 (437–1053)	594 (384–870)	0.003
Epinephrine, pg/mL	26 (14–46)	41 (22–62)	23 (12–39)	<0.001
Medications, n (%)				
ACE-inhibitor or ARB	315 (51.8)	72 (51.8)	243 (51.8)	0.51
Beta-blocker	322 (52.7)	73 (52.5)	249 (52.8)	0.99
Loop diuretic	344 (56.3)	81 (58.3)	263 (55.7)	0.59
Spironolactone	157 (25.7)	44 (31.7)	113 (23.9)	0.067
Digoxin	81 (13.3)	17 (12.2)	64 (13.6)	0.68
Antidepressant	22 (3.6)	7 (5.1)	15 (3.2)	0.30
Hypnotic drug	154 (25.2)	43 (30.9)	111 (23.6)	0.079

Values are mean ± standard deviation, percentages, or median (interquartile range, IQR). BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein; HbA1c = hemoglobin A1c; ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker.

delirium, who were more likely to have mechanical ventilation, noninvasive positive pressure ventilation, continuous hemodiafiltration, and inotropes than those without.

Median hospital stay was 20 days (IQR: 14–28). Patients with delirium had a longer hospital stay than those without (23 vs. 19 days, p = 0.007). During hospitalization, there were 12 all cause deaths, 7 cardiovascular deaths, 5 non-cardiovascular deaths and 51 worsening HF. There was no significant difference in the incidence of all-cause death between the two groups although there was a trend toward a higher incidence of all-cause death in patients with delirium (p = 0.11). The incidence of non-cardiovascular death and worsening HF was significantly higher in patients with delirium than in those without (Table 3). In univariate analysis, delirium, eGFR, systolic blood pressure, use of invasive procedure or inotropes, CICU admission and log BNP were significant determinants of worsening HF during hospitalization. In multivariate logistic regression analysis, delirium, as well as eGFR and systolic blood pressure, was an independent determinant of worsening HF during hospitalization (Table 4).

Among patients who survived until discharge, the prevalence of difficulty walking or a bedridden state was significantly higher in patients with delirium than in those without (30.6% vs. 11.3%, p < 0.001). In addition, patients with delirium were more likely to require subsequent placement in a nursing home after discharge (54.4% vs. 23.3%, p < 0.001), hypotonic drugs (39.1% vs. 26.9%, p = 0.007) and antidepressants (10.5% vs. 4.1%, p = 0.004) at discharge than those without, while there were no significant differences between the groups in the use of ACE-inhibitors or ARBs, beta-blockers (73.7% vs. 70.1%, p = 0.42), loop diuretics (76.7% vs. 81.5%, p = 0.21), spironolactone (40.3% vs. 39.8%, p = 0.91) and digoxin (10.5% vs. 14.1%, p = 0.27) at discharge.

3.3. Long-term clinical outcomes after discharge

During the median follow-up period of 335 days (IQR: 147–545), 50 all-cause deaths, 39 cardiovascular deaths, 19 non-cardiovascular deaths and 109 cases of worsening HF occurred after discharge. Kaplan–Meier analyses revealed that patients with delirium experienced a higher incidence of all-cause death, cardiovascular death, and non-cardiovascular death than those without. There was no significant difference in the incidence of readmission for HF between the two

Table 3
Treatment and outcomes during hospitalization.

Variable	Overall (n = 611)	Delirium (n = 139)	No delirium (n = 472)	p value
CICU admission, n (%)	274 (44.8)	78 (56.1)	196 (41.5)	0.003
Treatment during hospitalization, n (%)				
Mechanical ventilation	16 (2.7)	15 (11.1)	1 (0.2)	<0.001
NPPV	139 (22.9)	44 (31.9)	95 (20.3)	0.004
CHDF	11 (1.8)	9 (6.5)	2 (0.4)	<0.001
Inotropes	90 (14.7)	34 (24.5)	56 (11.9)	0.002
Diuretics	442 (72.9)	107 (77.5)	335 (71.6)	0.17
Coronary angiography	151 (25.2)	27 (20.2)	124 (26.7)	0.12
PCI	26 (4.3)	9 (6.5)	17 (3.6)	0.14
Length of hospital stay, days	20 (14–28)	23 (15–36)	19 (14–28)	0.007
In-hospital events, n (%)				
All cause death	12 (2.0)	5 (3.6)	7 (1.5)	0.11
Cardiovascular death	7 (1.2)	2 (1.4)	5 (1.1)	0.71
Non-cardiovascular death	5 (0.8)	3 (2.2)	2 (0.4)	0.046
Worsening heart failure	51 (8.3)	24 (17.3)	27 (5.7)	<0.001

Values are percentages or median (interquartile range, IQR). CICU = cardiovascular intensive care unit; NPPV = noninvasive positive pressure ventilation; CHDF = continuous hemodiafiltration; PCI = percutaneous coronary intervention.

Table 4
Logistic regression analysis for determinants of worsening heart failure during hospitalization.

Variable	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Delirium	3.44	1.90–6.19	<0.001	2.44	1.27–4.63	0.008
eGFR: per 10 mL/min/1.73 m^2 increase	0.68	0.58–0.80	<0.001	0.72	0.60–0.86	0.001
Systolic BP: per 10 mm Hg increase	0.85	0.76–0.93	0.001	0.88	0.79–0.98	0.019
Invasive procedure or inotropes administration[a]	2.45	1.37–4.42	0.003	1.85	0.96–3.59	0.07
CICU admission	1.83	1.03–3.32	0.041	1.44	0.96–3.59	0.27
Log BNP	1.56	1.14–2.16	0.007	1.08	0.77–1.52	0.66
Sodium	0.94	0.89–1.00	0.06	–	–	–
LVEF	0.99	0.97–1.01	0.19	–	–	–
History of cerebrovascular disease	0.51	0.22–1.05	0.09	–	–	–
Serum albumin: per 0.2 g/dL increase	0.94	0.83–1.07	0.35	–	–	–
NYHA class III or IV	1.40	0.54–4.76	0.52	–	–	–
Age: per 10-year increase	0.92	0.74–1.16	0.44	–	–	–
Blood glucose: per 10 mg/dL increase	1.02	0.98–1.06	0.36	–	–	–
Female	0.84	0.45–1.52	0.57	–	–	–
BMI	0.99	0.92–1.06	0.80	–	–	–

OR = odds ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; BP = blood pressure; CICU = cardiovascular intensive care unit; BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; BMI = body mass index.
[a] Invasive procedure or inotropes administration = use of at least one of the following therapy: mechanical ventilation, continuous hemodiafiltration, percutaneous coronary intervention, coronary angiography, and intravenous administration of inotropes.

groups (Fig. 1A–D). Univariate Cox proportional hazards model analysis showed that delirium, serum albumin level, body mass index, systolic blood pressure, age, serum sodium level and eGFR were significant determinants of all-cause death. The other variables, including CICU admission, use of invasive procedure or inotropes, history of cerebrovascular disease, NYHA class III or IV, BNP level, blood glucose level, female gender and LVEF, were not significant. In the multivariate model, the development of delirium was confirmed to be an independent determinant of all-cause death after discharge (Table 5).

3.4. Determinants of delirium

Table 6 shows the results of univariate and multivariate logistic regression analyses for the determinants of delirium development. In

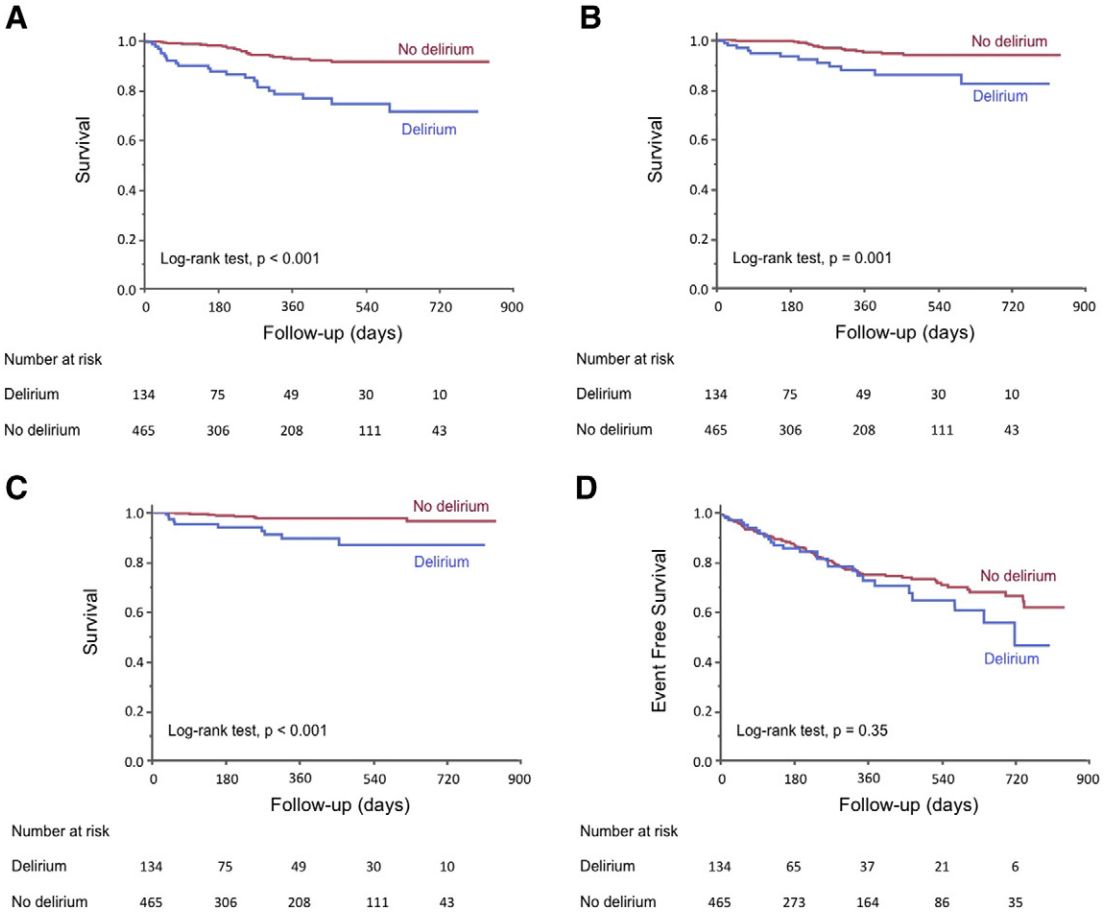

Fig. 1. Kaplan–Meier analyses of clinical outcomes after discharge in patients with or without delirium. A, all-cause death. B, cardiovascular death. C, non-cardiovascular death. D, worsening heart failure.

Table 5
Cox proportional hazards model for determinants of all-cause death after discharge.

	Univariate			Multivariate		
Variable	HR	95% CI	p value	HR	95% CI	p value
Delirium	3.58	2.03–6.28	<0.001	2.38	1.30–4.35	0.005
Serum albumin: per 0.2 g/dL increase	0.70	0.62–0.80	<0.001	0.78	0.68–0.90	0.001
BMI	0.85	0.78–0.93	<0.001	0.89	0.81–0.98	0.016
Systolic BP: per 10 mm Hg increase	0.85	0.77–0.94	0.002	0.90	0.81–0.99	0.043
Age: per 10-year increase	1.43	1.10–1.93	0.013	1.21	0.91–1.63	0.19
Sodium	0.91	0.87–0.96	0.001	0.94	0.88–1.01	0.07
eGFR: per 10 mL/min/1.73 m^2 increase	0.85	0.73–0.98	0.029	0.93	0.80–1.09	0.38
CICU admission	1.70	0.96–2.99	0.06	–	–	–
History of cerebrovascular disease	1.36	0.72–2.45	0.32	–	–	–
NYHA class III or IV	1.61	0.65–5.36	0.36	–	–	–
Log BNP	1.13	0.84–1.53	0.42	–	–	–
Invasive procedure or inotropes administration[a]	0.99	0.55–1.75	0.42	–	–	–
Blood glucose: per 10 mg/dL increase	0.99	0.94–1.04	0.77	–	–	–
Female	0.80	0.42–1.45	0.48	–	–	–
LVEF	1.00	0.98–1.02	0.82	–	–	–

HR = hazard ratio; CI = confidence interval; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; CICU = cardiovascular intensive care unit; NYHA = New York Heart Association; BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; BMI = body mass index; LVEF = left ventricular ejection fraction.
[a] Invasive procedure or inotropes administration = use of at least one of the following therapy: mechanical ventilation, continuous hemodiafiltration, percutaneous coronary intervention, coronary angiography, and intravenous administration of inotropes.

the multivariate analysis, history of CVD, higher age, higher log BNP, lower serum albumin and higher blood glucose levels were independent determinants of the development of delirium.

4. Discussion

The major findings of this study were as follows: (i) Delirium developed in 23% of AHF patients during hospitalization, and the development of delirium was strongly and independently associated with higher incidence of worsening HF during hospitalization and higher all-cause mortality after discharge during the median follow-up period of 335 days. (ii) Patients with delirium had prolonged hospital stay, higher prevalence of difficulty walking or a bedridden state at discharge and higher incidence of nursing home placement after discharge than did those without. (iii) History of CVD, higher age, higher blood glucose and BNP levels, and lower serum albumin level were independent determinants of the development of delirium.

The incidence of delirium in hospitalized patients varies from 10 to 87%, depending on the population [5,16]. Of them, postoperative patients and those requiring mechanical ventilation have been reported to experience delirium frequently [17]. As shown in previous reports, delirium is observed in 17 to 35% of patients with hospitalized HF and is associated with higher short-term mortality and readmission for worsening HF [9,10]. Consistent with these reports, our study demonstrated that delirium was common and was associated with increased in-hospital worsening of HF. In addition, the present study provided several new findings. First, we demonstrated that delirium was significantly associated with higher long-term mortality after discharge including all-cause death, cardiovascular death and non-cardiovascular death (Fig. 1), although previous studies had shown only up to 90-day all-cause death and not mentioned the cause of death. Second, our study was based on data from a prospective registry that enrolled consecutive patients who were admitted with AHF, while previous studies had been based on the data from retrospective analyses of medical records. Therefore, our study not only provided detailed data (e.g. C-reactive protein, catecholamine levels and invasive procedures) that were not assessed in previous studies, but also showed that delirium remained a significant determinant of in-hospital worsening of HF and post-discharge death, even after adjustment for these detailed baseline characteristics which could affect clinical outcomes.

Several mechanisms could account for the association between the development of delirium and worse clinical outcomes. Firstly, since it is generally accepted that delirium is more likely to develop in patients with severe illness [18], the development of delirium may reflect the severity of underlying illness. In fact, the present study demonstrated that patients with delirium had more severe baseline characteristics and were more likely to receive invasive therapies during hospitalization than those without. Nevertheless, our findings as well as those in previous studies showed that delirium remains an independent determinant of worse clinical outcomes, even after adjusting for many potential confounding factors related to disease severity [3,19]. Therefore, delirium is probably not merely a marker of underlying disease severity, but may worsen the prognosis. Secondly, the development of delirium may lead to decreased compliance with the treatment of HF, such as difficulty in taking oral medications, fluid intake restriction and staying in bed, and unplanned self-extubation, which can cause prolonged hospitalization, worsening HF, and increased mortality [20].

Table 6
Determinants of development of delirium.

	Univariate			Multivariate		
Variable	HR	95% CI	p value	HR	95% CI	p value
History of cerebrovascular disease	2.19	1.46–3.29	<0.001	2.13	1.36–3.35	0.001
Age: per 10-year increase	1.58	1.31–1.93	<0.001	1.43	1.15–1.80	0.001
Log BNP	1.45	1.18–1.79	0.001	1.39	1.09–1.79	0.009
Serum albumin: per 0.2 g/dL increase	0.80	0.75–0.89	<0.001	0.84	0.76–0.93	0.001
BMI	0.94	0.89–0.98	0.01	0.99	0.93–1.05	0.69
Sodium	0.96	0.92–0.99	0.045	0.96	0.92–1.01	0.13
Blood glucose: per 10 mg/dL increase	1.05	1.02–1.08	0.001	1.03	1.00–1.06	0.048
eGFR: per 10 mL/min/1.73 m^2 increase	0.87	0.79–0.95	0.002	0.97	0.86–1.08	0.55

HR = hazard ratio; CI = confidence interval; BNP = brain natriuretic peptide; BMI = body mass index; eGFR = estimated glomerular filtration rate.

Thirdly, the development of delirium may lead to a decline in functional status due to long-term cognitive dysfunction, and worsen the prognosis of HF. Several studies have suggested that the development of delirium is associated with long-term cognitive dysfunction and may lead to a subsequent decline in functional status [3,21–24]. Consistent with previous reports, our study demonstrated that the functional status represented by difficulty walking or a bedridden state at discharge was significantly decreased in patients with delirium than in those without. Functional status has also been reported to be a key factor in quality of life and mortality in patients with HF [25], as well as those with other medical illnesses [26], and the general elderly population [27]. Fourthly, patients with delirium were more likely to be receiving hypotonic drugs at discharge, which might be related to increased non-cardiovascular mortality [28]. Furthermore, patients with delirium had higher use of antidepressant at discharge, while there were no significant differences in the prevalence of previous history of depression and use of antidepressants before admission. Therefore, newly developed depression might affect clinical outcomes in patients with delirium [29]. Otherwise, some patients with prolonged hypoactive delirium might be misdiagnosed as having depression, while the use of antidepressants for such patients might exacerbate their conditions [1]. Taking all these together, the development of delirium may result in worse clinical outcomes in patients with AHF.

Contrary to previous studies, there was no significant difference in the incidence of readmission for worsening HF between patients with and without delirium. The higher incidence of nursing home placement after discharge in patients with delirium might have led to close monitoring and early intervention, and result in the prevention of readmission for worsening HF.

Despite the fact that the precise pathophysiological mechanisms of delirium remain unclear, a number of factors are thought to result in disruption of neuronal networks in the brain, leading to acute cognitive dysfunction. The present study showed that a history of CVD, higher age, and hypoalbuminemia were independent determinants of the development of delirium. These factors are associated with patient frailty and have been reported to increase baseline delirium vulnerability [1,18,30,31]. Our study also demonstrated that higher BNP and hyperglycemia were significant determinants of the development of delirium. Higher BNP and hyperglycemia may be related to elevation of sympathetic nerve activity [32]. In addition, plasma levels of catecholamines including dopamine, norepinephrine and epinephrine on admission were significantly higher in our patients with delirium than in those without. These results imply an association between elevated sympathetic nerve activity and the development of delirium and provide the hypothesis that administration of sympathetic nerve-blocking agents such as β-blockers may reduce the risk of development of delirium in patients with AHF. Alternatively, BNP is an established biomarker of HF severity [33], and severity of HF has been reported to be associated with decreased cerebral perfusion and cognitive impairment [34–36]. Because impaired cerebral perfusion has been reported to be associated with the development of delirium [37,38], patients with higher BNP levels may be vulnerable to the development of delirium due to decreased cerebral perfusion.

Our study has several clinical implications. The present findings indicated that delirium is a common, serious problem in patients with AHF. It is noteworthy that delirium can be prevented in 30–40% of cases through multicomponent interventions [39–41]; therefore, earlier detection and treatment of delirium are highly recommended [1,12]. Nevertheless, delirium is often unrecognized in clinical practice due to its fluctuating course [42]. Indeed, it has been reported that up to 76% of delirium cases may be underdiagnosed without active monitoring [43,44]; therefore, routine active monitoring of delirium may be recommended in AHF patients. Furthermore, it is important to modify patients' environment, including reducing psychoactive medication and introducing bedside cardiac rehabilitation, especially in patients at risk of development of delirium [12,45]. These efforts to prevent the development of delirium may lead to a better prognosis in patients with AHF.

This report has a number of limitations. First, the present study was a single-center observational study. Therefore, some information that might affect the outcome and incidence of delirium was unavailable or incomplete, such as cognitive function, use of antipsychotic drugs and functional status before admission. Second, although we used ICDSC for the diagnosis of delirium, the most appropriate method for screening for delirium in AHF patients remains unclear.

In summary, AHF patients who developed delirium had unfavorable clinical outcomes, particularly a higher incidence of worsening HF during hospitalization and higher mortality after discharge. Patients with a history of cerebrovascular disease, higher age, higher BNP level, hypoalbuminemia and hyperglycemia on admission were susceptible to delirium development and should be under careful monitoring during hospitalization.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

For supplemental material including a list of investigators, clinical research coordinators and data managers, please see the online version of this article. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ijcard.2016.07.236.

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