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

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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.

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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.