

# 学位論文の要旨

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学位論文名 Delirium is Associated With High Mortality in Older Adult Patients With Acute Decompensated Heart Failure

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## 論文内容の要旨

### **INTRODUCTION**

Delirium is characterized by a disturbance in consciousness. It is commonly encountered in a variety of clinical settings. The number of patients with acute decompensated heart failure (ADHF) has recently been increasing worldwide. It is important to investigate appropriate ways to manage delirium because this condition is associated with a poor prognosis. Postoperative delirium in the context of cardiac surgery, is associated with higher mortality rates. However, only a few studies have investigated the relationship between delirium and prognosis in patients with ADHF.

The prognosis of patients with delirium depends on its subtype, which is divided into 3 categories: hyperactive, hypoactive, and mixed. The prognosis of patients with hypoactive delirium is worse than that of patients with hyperactive delirium. Evidence on the prognosis of each subtype has not been fully established in patients with ADHF. The objective of this study was to investigate the prognostic impact of delirium on mortality and risk factors for delirium.

### **MATERIAL AND METHODS**

This single-center prospective observational study enrolled 132 consecutive adult patients admitted with ADHF at Shimane University Hospital. We defined ADHF as rapid worsening of heart failure symptoms with a need for hospitalization. The presence of

delirium and its subtype was assessed every day for 14 days after the hospitalization using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM–5). Hyperactive delirium is described as a disruptive behavior such as restlessness; hypoactive delirium is described as a decreased amount of activity, such as listlessness; and mixed delirium has both features.

The primary endpoint was set as the 90-day all-cause mortality and the secondary endpoint as the cumulative incidence of delirium from the day of admission. The incidence of each subtype of delirium was also recorded. The study population was classified into two groups according to the presence or absence of delirium during hospitalization to assess the prognostic impact of delirium. Kaplan–Meier analysis was employed to estimate the 90-day all-cause mortality. The prognostic impact of delirium and risk factors associated with delirium were evaluated using Cox regression and logistic regression analyses, respectively. All statistical analyses were conducted using Microsoft R Open version 3.3.2, and p-values of <0.05 were considered statistically significant. The study protocol complied with the Helsinki Declaration standards and was approved by the institutional review board of Shimane University Hospital.

## **RESULTS AND DISCUSSION**

The median age of the study population was 83 (IQR, 75–87) years, and 51.5% of the patients were men. Approximately 27.3 % of the patients had dementia. The median brain natriuretic peptide (BNP) level was 601 (331–1,264) pg/mL. A total of 36 (27.3%; 95% CI, 19.3–34.5) patients developed delirium within 14 days of their hospital admission. The patients with delirium were significantly older and had a higher incidence of dementia. BNP level was significantly higher in patients with delirium compared with patients without delirium.

Most patients developed hyperactive delirium (86.1%), followed by mixed delirium (8.3%), and hypoactive delirium (5.6%). The 90-day mortality was significantly higher in the patients with delirium (21.6%; 95% CI, 3.4–36.4) than in those without (3.9%, 95% CI 0.0–8.3), at a log–rank p-value of 0.002. In addition, the multivariable Cox regression analysis revealed that delirium was independently associated with the 90-day all-cause mortality, with a hazard ratio (HR) of 6.8 (95% CI, 1.1–42.6; p=0.042). The multivariable logistic regression analysis demonstrated that older age and presence of dementia (adjusted OR, 3.3; 95% CI, 1.1–10.4; p=0.040) were associated with the development of delirium after hospitalization owing to ADHF.

In the present study, the major findings included the following: 1) The incidence of delirium in this study was 27.3%, 2) hyperactive delirium was the most common subtype;

3) delirium was associated with increased mortality; and 4) the independent risk factors for delirium in the patients with ADHF were older age and dementia.

The incidence of delirium in this study was slightly higher than that in previous retrospective studies which reported 17–23%. This can be attributed to the advanced age of our study population. It is notable that hyperactive delirium was the most common subtype (86.1%) in this study. We speculated that impaired circadian rhythm and expansion of neuroinflammation in patients with ADHF might be associated with the increased incidence of hyperactive delirium. We showed that the prognosis of the patients with ADHF who developed delirium was worse than that of those without delirium. Delirium was independently associated with the 90-day all-cause mortality in the present study. Uthamalingam et al. and Honda et al. reported that the adjusted HRs for the presence of delirium in relation to the all-cause mortality were 2.10 (95% CI, 1.53–2.88,  $p < 0.0001$ ) at 90 days and 2.38 (95% CI, 1.30–4.35,  $p = 0.005$ ), respectively. Our results are consistent with these reports in view of the high risk of delirium in association with mortality. Regarding the risk factors of delirium, advanced age and dementia were associated with the occurrence of delirium in this study. These risk factors have been proven with sufficient evidence and it is notable that advanced age remained as a risk factor even in this advanced-aged study population. Our data contribute to better understanding of delirium in patients with ADHF, and it is noteworthy that hyperactive delirium was the most common subtype observed in the present study. Physicians should consider delirium when treating ADHF, and evaluation of early occurrence of and accurate diagnosis of delirium in relation to the prognosis in patients with ADHF should be strongly considered in future trials.

There are several limitations in the present study. The effect of delirium subtype on mortality could not be assessed in the current study due to the limited number of patients. The relationship between delirium and sedative–hypnotic drug use could not be assessed because the decision for administration of such drugs for the patients depended on the individual judgment of each attending physician.

### **CONCLUSION**

Delirium was associated with a higher 90-day all-cause mortality in the patients with ADHF. Hyperactive delirium was the most common subtype according to the DSM–5.