ORIGINAL RESEARCH

Delirium in hemodialysis predicts mortality: a single-center, long-term observational study

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Objectives: Delirium signifies underlying brain dysfunction; however, its clinical significance in hemodialysis remains unclear. In this study, we sought to determine whether the occurrence of delirium during hemodialysis was associated with higher mortality.

Patients and methods: This was a retrospective, 10-year cohort study. This study was performed at the urology department located within a hospital in Oyokyo, Hirosaki. We analyzed 338 of 751 patients who underwent hemodialysis. Psychiatrists diagnosed patients with delirium according to the corresponding DSM-IV-TR criteria. Cox proportional hazard regression, which was adjusted for patient age at the time of hemodialysis initiation, sex, and the presence of diabetes mellitus, was performed. Hazard ratios (HRs) and their 95% CIs were also reported.

Results: In total, 286 patients without psychiatric diseases and 52 patients with delirium were evaluated. Eighty percent of patients with delirium died within 1 year of hemodialysis initiation, while only 22% of patients without delirium died within the same time period ($P<0.01$). Kaplan–Meier plots demonstrated the existence of associations between delirium and all-cause mortality (global log-rank $P<0.001$), cardiovascular disease-related mortality (global log-rank $P<0.001$), and infection-related mortality (global log-rank $P<0.001$). Moreover, Cox proportional hazard regression showed that delirium was associated with all-cause mortality (HR=1.96, 95% CI: 1.32–2.90), cardiovascular disease-related mortality (HR=2.65, 95% CI: 1.31–5.35), and infection-related mortality (HR=3.30, 95% CI: 1.34–8.10).

Conclusion: Delirium is an independent predictor of death in patients undergoing hemodialysis.

Keywords: delirium, hemodialysis, mortality, observational study, disturbance of consciousness

Introduction

Delirium is a neurobehavioral syndrome characterized by fluctuating or abnormal mental status and inattention as well as an altered level of consciousness or disorganized thinking.[1] Delirium is a common complication affecting patients in the intensive care unit[2] and is associated with higher mortality, prolonged hospitalization, and long-term cognitive impairment.[3,4] Clinicians have attributed the disease to several phenomena, including neurotransmitter imbalances, sleep–wake cycle disruption, metabolic abnormalities, and stress responses;[5] however, the pathogenesis of delirium remains unclear.

Chronic kidney disease affects ~10%–15% of adults globally and increases the risk of death by ~2–4-fold in affected patients, compared with that in unaffected patients. This increase has been attributed mostly to increased cardiovascular disease-related mortality.[6–9] Patients with stage 5 chronic kidney disease who are receiving dialysis treatment display a particularly heavy symptom burden. Specifically, these patients develop fatigue, anxiety and depression, sleep disturbances, and itching.[10]

Delirium is commonly observed in patients undergoing dialysis. It has been attributed to electrolyte imbalances that occur after dialysis, which cause a phenomenon known as dialysis disequilibrium syndrome (DDS), or because of medical or surgical complications.[11,12] Delirium may also be caused by uremia, anemia, and hyperparathyroidism.

Few studies, however, have explored whether the presence of delirium is associated with mortality in patients undergoing hemodialysis over a long-term observation period. Therefore, we assessed patients with known psychiatric diagnoses of delirium and examined the association between delirium and mortality in a cohort of patients undergoing maintenance hemodialysis over 10 years of observation.

Patients and methods
Study sample and group assignment
The study protocol was approved by the Ethics Committee of Hirosaki University on Human Research. Informed consent was obtained from all patients. None of the patients refused to participate in the retrospective study. Between 2006 and 2015, 751 consecutive patients undergoing hemodialysis were approached and asked for their consent to collect their clinical data for research purposes, retrospectively. Of these 751 eligible patients, 492 received an early psychiatric diagnostic assessment, 346 did not exhibit symptoms of psychiatric disease, and 146 displayed symptoms of

psychiatric disease (Figure 1). Among 146 patients, 39 who presented with delirium upon initiation, as determined by trained psychiatrists according to the corresponding DSM-IV criteria, were eligible for the study. Moreover, the remaining 107 patients displaying symptoms of psychiatric disease, whose diagnoses included dementia (n=39), insomnia (n=25), depression (n=19), and other psychiatric diseases (n=24; epilepsy, schizophrenia, neuropathic pain, adjustment disorder, and panic disorder), were excluded from the analyses. After hemodialysis initiation, 60 of the abovementioned 346 patients without a previous history of psychiatric symptoms or disease exhibited symptoms of psychiatric disease. Thirteen of these patients received diagnoses of delirium, according to the criteria specified by the DSM-IV and, thus, were included in the study. The remaining 47 patients, whose diagnoses included dementia (n=20), insomnia (n=10), depression (n=8), and other psychiatric diseases (n=9; epilepsy, schizophrenia, neuropathic pain, and adjustment disorder), were excluded from the analyses. Thus, 286 healthy patients and 52 patients with delirium were ultimately included in this study.

We obtained demographic data (age, sex) and information pertaining to clinical diagnoses by reviewing the Oyokyo Hospital database and patient medical records (Table 1). Data regarding overall and specific mortality rates were obtained from the clinical database and patient death certificates. Cardiovascular
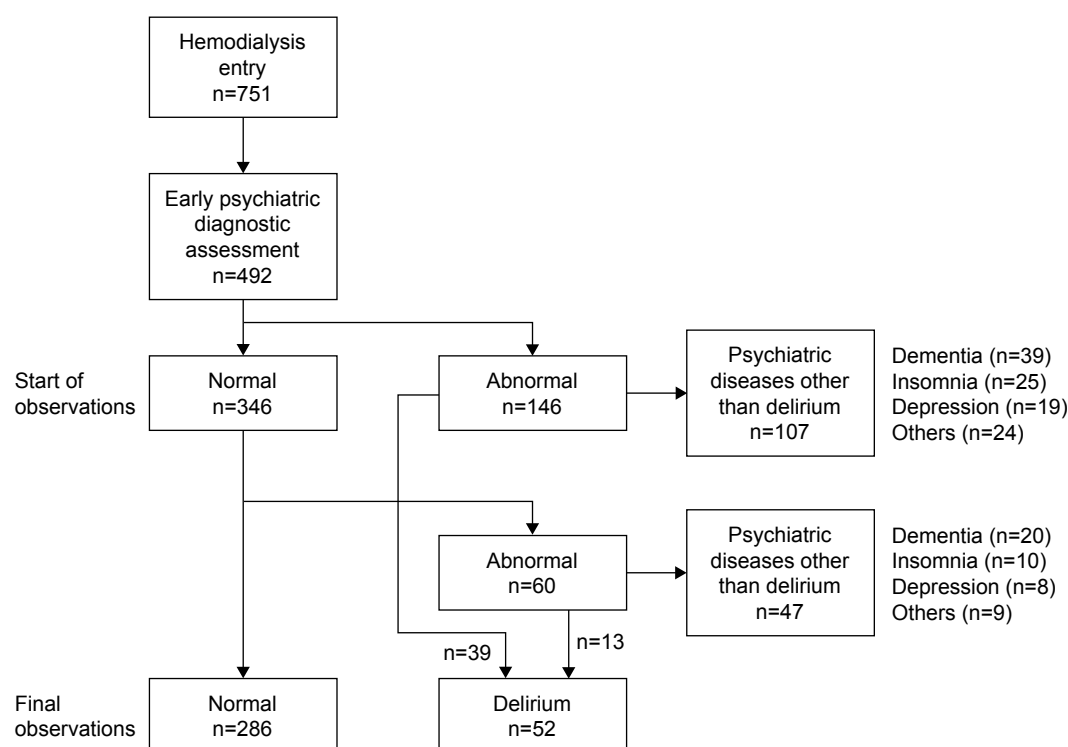

Figure 1 Flow chart of patient inclusion in the study.

Table 1 Patient characteristics

	Control, n=286 (%)	Delirium, n=52 (%)	Significance, P-value
Age at entry (years)[a]	65.8±12.7	75.4±8.1	<0.001
Male sex	188 (66)	29 (56)	0.168
Duration of hemodialysis (days)[a]	825±806	884±814	0.623
Primary indication of hemodialysis			
Diabetes	174 (60.8)	27 (51.9)	
Hypertension	23 (8.0)	5 (9.6)	
Glomerulonephritis	20 (7.0)	1 (1.9)	0.206
Others	25 (8.7)	5 (9.6)	
Unknown	44 (15.4)	14 (26.9)	
Primary cause of death	n=81	n=39	
Cardiovascular disease	21 (25.9)	14 (36.8)	
Infection	10 (12.3)	10 (26.3)	
Cancer	13 (16.0)	1 (2.6)	<0.001
Others	19 (23.5)	13 (34.2)	
Unknown	18 (22.2)	0 (0.0)	

Note: [a]Data shown as mean ± SD.

disease-related causes of death included sudden death or acute myocardial infarction-related death; pericarditis; atherosclerotic heart disease; cardiomyopathy; cardiac arrhythmia; cardiac arrest; valvular heart disease; pulmonary edema; congestive cardiac failure; cerebrovascular accidents, including intracranial hemorrhage; and ischemia-induced brain injury-related phenomena, including anoxic encephalopathy. The primary outcomes of the study, which were defined a priori, were all-cause mortality and death due to cardiovascular disease-related causes and infection-related mortality. Patients were followed until their death. Survival time was defined as the period between each patient's initial enrollment (starting hemodialysis) in the study and his or her death or December 31, 2015.

Statistical analysis

The descriptive characteristics of the study population were reported as proportions in the case of categorical and binary variables, means and SDs in the case of continuous normally distributed variables, and medians with interquartile ranges in the case of skewed variables. Differences between categorical variables were assessed using chi-squared tests. Mortality rates were calculated by dividing the number of deaths in each group by the total accrued person-time in each group. Kaplan–Meier plots for time to death were constructed for the healthy patient and delirium patient groups, and the log-rank test was used to determine the difference in survival between the healthy patient and delirium patient groups. Cox proportional hazards regression models were used to assess the association between the presence of delirium and all-cause mortality, cardiovascular-related mortality, and infection-related mortality, and nested models were used to perform adjustments for demographics (age, sex, and the presence of

diabetes). A P-value <0.05 was regarded as statistically significant. The covariates served as time-dependent variables. All analyses were performed using SPSS, version 24.

Results

Two hundred eighty-six patients without psychiatric disease and 52 patients with delirium were analyzed. The group of patients with delirium was significantly older than the group of patients without delirium (P<0.001; Table 1). The average duration of hemodialysis was not different between the patients with delirium and those without delirium (Table 1). Our results showed no sex distribution between the delirium group and the healthy group (Table 1). No difference in the frequency of underlying disease was found between the healthy group of patients and the group of patients with delirium; however, there was a significant difference between the two groups with respect to the incidence of specific causes of death (P<0.01; Table 1). There was no difference in characteristic data between the early detection group (n=39) and the late detection group (n=13; data not shown). Delirium was treated with antipsychotics such as haloperidol (n=25), risperidone (n=15), quetiapine (n=10), levomepromazine (n=10), perospirone (n=5), and blonanserin (n=4) and antidepressants such as trazodone (n=3) and mianserin (n=1). The analysis showed that 80% of patients with delirium died within 1 year of dialysis initiation, while only 22% of patients without delirium died during the same period (P<0.01).

Figure 2 displays the unadjusted all-cause survival curves for the patients with and without delirium. The Kaplan–Meier plots demonstrated the existence of an association between
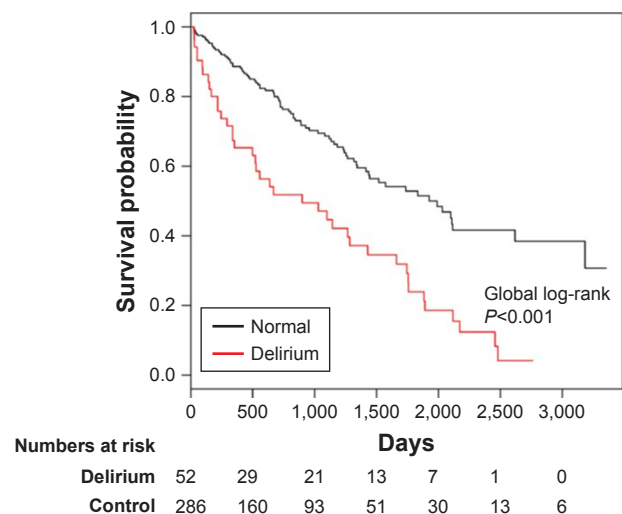

Numbers at risk							
Delirium	52	29	21	13	7	1	0
Control	286	160	93	51	30	13	6

Figure 2 Unadjusted all-cause survival curves for patients with and without delirium.
Note: The black line represents the survival curve for patients without delirium, and the red line represents the survival curve for patients with delirium.

Table 2 Cox regression model for all-cause mortality, cardiovascular-related mortality, and infection-related mortality

	All-cause mortality		Cardiovascular-related mortality		Infection-related mortality	
	Crude model	Adjusted model	Crude model	Adjusted model	Crude model	Adjusted model
Presence of delirium	2.42 (1.66–3.53)*	1.96 (1.32–2.90)**	3.36 (1.71–6.64)***	2.65 (1.31–5.35)**	5.14 (2.13–12.37)***	3.30 (1.34–8.10)**
Age		1.05 (1.03–1.07)***		1.09 (1.05–1.14)***		1.11 (1.05–1.17)***
Male sex		1.86 (1.26–2.73)**		1.77 (0.87–3.62)		1.55 (0.62–3.91)
Diabetes (as an indication of hemodialysis)		1.24 (0.84–1.83)		1.75 (0.84–3.66)		1.15 (0.45–2.96)

Notes: All variables are hazard ratio and 95% CI. *$P<0.05$, **$P<0.01$, ***$P<0.001$.

the presence of delirium and all-cause mortality (global log-rank $P<0.001$), and Cox proportional hazard regression showed that all-cause mortality was associated with the presence of delirium (hazard ratio [HR] =1.96, 95% CI: 1.32–2.90), age (HR=1.05, 95% CI: 1.03–1.07), and male sex (HR=1.86, 95% CI: 1.26–2.73), but not the presence of diabetes (HR=1.24, 95% CI: 0.84–1.83), as shown in Table 2. Figure 3 displays the unadjusted cardiovascular disease-related survival curves for the patients with and without delirium. The Kaplan–Meier plots demonstrated the existence of an association between the presence of delirium and cardiovascular disease-related mortality (global log-rank $P<0.001$). Cox proportional hazard regression showed that cardiovascular disease-related mortality was associated with the presence of delirium (HR=2.65, 95% CI: 1.31–5.35) and age (HR=1.09, 95% CI: 1.05–1.14), but not sex (HR=1.77, 95% CI: 0.87–3.62) or the presence of diabetes (HR=1.75, 95% CI: 0.84–3.66), as shown in Table 2. Figure 4 displays the unadjusted infection curves for the patients with and without delirium. The Kaplan–Meier

plots demonstrated the existence of an association between the presence of delirium and infection-related mortality (global log-rank $P<0.001$). Cox proportional hazard regression showed that infection-related mortality was associated with the presence of delirium (HR=3.30, 95% CI: 1.34–8.10) and age (HR=1.11, 95% CI: 1.05–1.17), but not sex (HR=1.55, 95% CI: 0.62–3.91) or the presence of diabetes (HR=1.15, 95% CI: 0.45–2.96), as shown in Table 2.

Discussion

There are limited data regarding the relationship between delirium and mortality in patients undergoing hemodialysis. In this longitudinal study, which examined the relationship between delirium and mortality in patients undergoing maintenance dialysis, the presence of delirium was found to be associated with an increased risk of mortality. The relationships between delirium and all-cause and cardiovascular- and infection-related mortality were attenuated by adjustments for demographics, but remained significant after adjustments for age, sex, and comorbidity of diabetes.
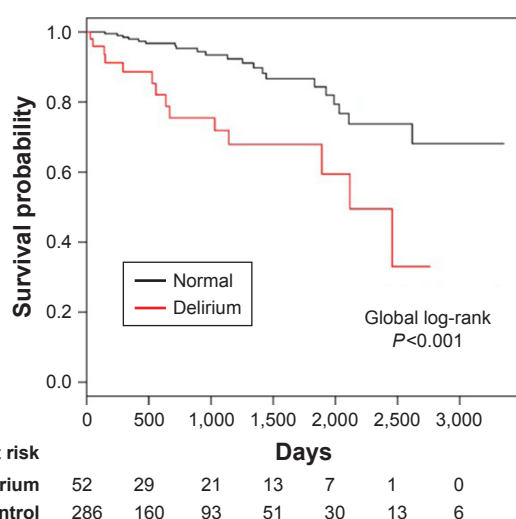

Figure 3 Unadjusted cardiovascular disease-related survival curves for patients with and without delirium.
Note: The black line represents the survival curve for patients without delirium, and the red line represents the survival curve for patients with delirium.
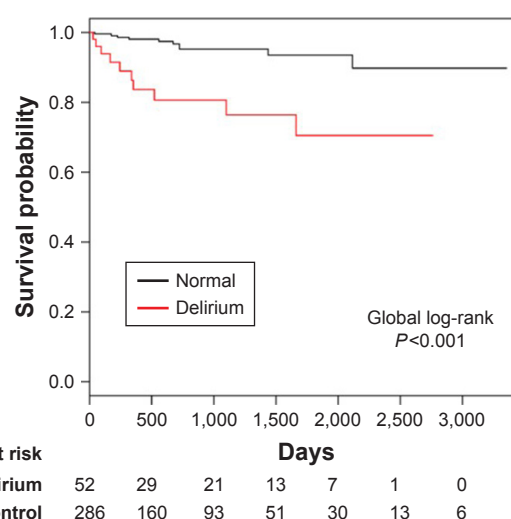

Figure 4 Unadjusted infection-related survival curves for patients with and without delirium.
Note: The black line represents the survival curve for patients without delirium, and the red line represents the survival curve for patients with delirium.

It is difficult to distinguish between DDS, which is an adverse effect of acute hemodialysis in advanced uremic patients and is caused by brain edema,[12] and delirium because some symptoms are very similar. DDS is reversible,[12] whereas most patients died even in early detection delirium groups in the study. Therefore, it is unlikely that many subjects with DDS were included in the study, although we did not confirm DDS using brain imaging.

In this study, we noted significant associations between delirium and cardiovascular- and infection-related mortality. Medications such as antipsychotics may be useful in ameliorating delirium.[13] However, most antipsychotics have an unfavorable cardiovascular side effect profile, and sudden cardiac death may occur even in patients with no cardiovascular disease risk factors. Currently, most clinicians are focusing on antipsychotic-induced corrected QT prolongation because this phenomenon may increase the risk of Torsades de Pointes and, eventually, sudden cardiac death. Other cardiovascular diseases attributed to antipsychotic use include the Bragada syndrome phenotype, myocardial infarction, and myocarditis.[14] In addition, antipsychotic use was associated with a higher risk of pneumonia in an Alzheimer's disease cohort and a somewhat higher risk of pneumonia in a non-Alzheimer's disease cohort.[15] Therefore, using antipsychotics as a standard treatment for delirium may lead to cardiovascular- and infection-related mortality.

Two studies explored the association between dementia, which was diagnosed via reviews of medical charts or billing codes, and mortality. Both studies noted that dementia was an independent risk factor for mortality.[16,17] Based on these findings, we excluded patients with dementia from this study. Patients undergoing hemodialysis exhibit impairment in multiple cognitive function domains; however, executive function, which is critical for planning and performing tasks, appears to be affected more than other domains, such as memory.[18] Our previous study showed that undergoing hemodialysis was a significant independent risk factor for lower Mini Mental State Examination scores.[19] The causes of cognitive impairment in patients undergoing dialysis appear to be multifactorial;[20] however, cerebrovascular disease is likely an important cause of such impairment[21] because it often affects brain structures related to executive function.[22]

In this study, male sex was associated with all-cause and cardiovascular disease-related mortality. Three previous studies[18,23,24] analyzed the risk of mortality in adult male versus female patients undergoing hemodialysis. Carrero et al used the large dataset of the European Renal Association European Dialysis and Transplant Association registry and found that younger women have a higher risk of dying from noncardiovascular causes than younger men.[23] This finding could not be confirmed in this study involving patients receiving maintenance hemodialysis because the incidence of specific causes of death among patients aged 18–44 years did not differ significantly between men and women.

We excluded depression from the analysis because we aimed to exclude any non-delirium factors influencing mortality from the study; however, the prevalence of depression in patients undergoing dialysis appears to range from 15% to 30%, depending on the methodology used to diagnose depression and demographics of the populations under study.[25,26] Several previous studies whose cumulative population exceeded that of existing studies showed that an association exists between depression and cardiovascular mortality in adults with kidney failure.[27–29]

The findings of this study should be interpreted with caution for several reasons. First, the single-center longitudinal design of the study did not allow us to make causal assumptions regarding the relationship between delirium and mortality. Future multicenter longitudinal studies are needed to investigate these associations. Second, several potential confounding factors, such as physical activity levels, socioeconomic status, lifestyle, electrolyte abnormalities, body mass index, blood pressure, hemoglobin, albumin levels, and renal function, were not assessed in our study. Future studies adjusting for these confounders are needed. Third, early psychiatric diagnostic assessments were not performed in all patients because some of the patients were too ill to undergo a psychiatric examination. Therefore, some of the patients who were excluded from the study may have had more severe disease than those who were ultimately included in the study. Finally, as our sample size was relatively small, we could not completely rule out beta error as the reason for not detecting associations, such as the presence of diabetes, between the presence of delirium and mortality.

Conclusion

The presence of delirium has a significant and negative impact on mortality among patients undergoing hemodialysis. Physicians must promote early screening and the best preventive practices to ensure that affected patients receive optimal treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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