A retrospective study of factors associated with persistent delirium

Running title: Risk factors of delirium persistency

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Abstract

Background

It has been reported that delirium causes various problems. Many researchers have reported the risk factors associated with the onset of delirium, however, there are few reports focused on persistent delirium. This study aimed to identify the risk factors associated with persistent delirium.

Methods

A total of 573 patients hospitalized in Nara Prefecture General Medical Center from October 2014 through September 2017 who were referred to the psychiatry consultation service were included in this study. Persistent delirium was defined as delirium lasting for 14 days or more. A retrospective study was carried out based on the patients' records. The relationship between various background factors and persistent delirium was statistically analyzed.

Results

Of the 573 hospitalized patients, 295 were diagnosed as delirium. Forty-six patients with persistent delirium and 181 patients with nonpersistent delirium were included in this study. Multivariable logistic regression analyses revealed that male gender, opioid analgesics use, non-opioid analgesics use, and low serum sodium were significantly and independently associated with persistent delirium. Ramelteon or trazodone was used significantly more in persistent delirium, although each use was not significant.

Conclusion

This is the first study to reveal that male gender and use of analgesics were associated with persistent delirium in general hospital. However, as this is a case-control study and may contain bias, future cohort studies and intervention studies are needed. It is also necessary to investigate the relevance of the "degree of pain" behind the use of analgesics.

Keywords: delirium, persistent delirium, case-control study, general hospital, analgesic

Introduction

Delirium is a disorder of consciousness and attention with acute onset, characterized by its fluctuating condition. Its definition was updated in 2013 in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and includes acute disturbances in cognition and attention not fully explained by an underlying neurocognitive disorder.[1] The rate of developing delirium differs depending on age and underlying illness.[2,3] Delirium is reported to be found in 11% to 42% of cases of hospital stay[4] and causes impacts such as an increased rate of mortality, a heavier burden for nursing, and higher medical costs.[2,3,5,6,7] Regarding interventions, some effective strategies of non-pharmacological multicomponent approaches have been accepted,[8,9,10] while the effects of pharmacological interventions for delirium have been controversial.[2,11,12] Studies have shown that 30% to 40% of cases can be prevented by using low-tech, high-touch, and cost-saving interventions[2,9] ; therefore, investigating the factors that define the persistence of delirium might contribute to the prevention of its persistency.

Additionally, while delirium was thought to be a temporary episode with reversibility, a cohort study in Finland showed that delirium increased the risk of developing dementia, escalated its severity, and lowered overall functions of the patient after developing dementia.[13] Although many risk factors for delirium have been identified previously,[2,14,15] only a few studies have investigated the factors associated with persistent delirium.[16,17,18,19] Some delirium becomes persistent for terminal-phase cancer patients with a lower possibility of improvement in physical condition.[20] It has been reported that the persistence of delirium leads to a worsening of vital prognosis, lowering of cognitive function, and a higher possibility of requiring nursing-care services.[21,22] However, despite the expected impacts on patients' overall functions, there are few reports available about the persistence of delirium.

Herein, we conducted a retrospective study on delirium inpatients at Nara Prefecture General Medical Center intervened by psychiatrists to understand the background factors related to the persistence of delirium. A secondary objective was to assess whether the pharmacological interventions were associated with persistent delirium.

Methods

Ethics

This study was conducted with the approval of the Ethics Committee of the Nara Prefecture General Medical Center and due consideration to human rights of subjects, the protection of their privacy, and their ethical aspects. The opt-out documents have posted on the website.

Subjects

From October 2014 to September 2017, there were 573 cases referred to psychiatric consultations,

among them, we conducted retrospective study of 295 cases diagnosed with delirium (Figure 1). There were 180 male and 115 female patients, with an average age of 76.4 (range, 32–96) years. Patients with delirium continuing for 14 days and more are defined as having persistent delirium. Nonpersistent delirium is defined as delirium lasting for less than 14 days, excluding cases of death or outcomes of changing hospitals. Background factors we investigated are sex, age, dementia, cancer diagnosis, habit of drinking, use of benzodiazepine receptor agonist, use of opioid and non-opioid analgesics, and blood tests on admission to hospital (indicators of electrolyte abnormality are sodium and calcium, the indicator of inflammatory reaction is C-reactive protein, indicators of renal function are creatinine and estimated glomerular filtration rate (eGFR), and indicators of liver dysfunction are aspartate aminotransferase (AST) and alanine aminotransferase (ALT)). As a pharmacological intervention, we investigated the administration of typical antipsychotics, atypical antipsychotics, ramelteon, suvorexant, and trazodone.

Delirium was diagnosed based on the criteria under DSM-IV-TR and DSM-5 released by the American Psychiatric Association. There are four criteria for diagnosis of delirium: 1) disturbance of consciousness that lowers attention and concentration, 2) changes in cognition or disturbance of perception, 3) short-term development of conditions and daily fluctuations, and 4) evidence of causal physical abnormality. Each item of the background factors and the duration of delirium were retrospectively assessed using the patient's medical and nursing records.

Statistical analysis

Variables with normal distribution are reported as mean ± SD, and mean is compared between the persistent and nonpersistent delirium groups using an unpaired t-test. Asymmetrical distributed variables are shown as the median and interquartile ranges, and the Wilcoxon rank sum test was performed to compare the groups. As for dichotomous variables, the data are presented as percentages, and comparisons between the groups were performed using the chi-squared test. Crude odds ratios (ORs) with 95% CI for persistent delirium were estimated using a logistic regression model. ORs were simultaneously adjusted for age, sex, and variables (non-opioid analgesic use, opioid analgesic use, cancer diagnosis, serum ALT >23 [U/L] and serum Na < 138 [mEq/L]) that showed a significant association with persistent delirium in the univariate model. All statistical analyses were performed using R version 3.4.3, and $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics

A total of 227 delirium patients (mean age, 76.4±11.2 years; 143 men [63.0%]) were included in this study. Of these, 48 (21.1%) were classified as having persistent delirium. Compared with the

nonpersistent delirium group, the persistent delirium group showed a significantly higher ratio of non-opioid analgesic use (47.8 vs 8.3%, P < 0.001, Table 1), opioid analgesic use (21.7 vs 2.8%, P < 0.001), and cancer diagnosis (43.5 vs 20.4%, P = 0.002, Table 1); lower serum ALT (15.0 vs 19.0 U/L, P = 0.035, Table 1); and a lower serum sodium level ratio of less than 138 mEq/L (17.4 vs 39.2%, P = 0.009, Table 1).

Results of the crude or age-gender-adjusted logistic regression analysis

A crude logistic regression analysis revealed that the persistent delirium group was significantly associated with greater non-opioid analgesic use (crude OR: 10.1, 95% CI: 4.69–22.7, P < 0.001), greater opioid analgesic use (crude OR: 9.78, 95% CI: 3.27–33.0, P < 0.001), more patients diagnosed with cancer (crude OR: 2.99, 95% CI: 1.50–5.95, P = 0.002), lower serum ALT level (> 23 [U/L]; crude OR: 0.411, 95% CI: 0.183–0.852, P = 0.022), and lower serum sodium level (< 138 [mEq/L]; crude OR: 0.326, 95% CI: 0.135–0.707, P = 0.007) (Table 2, left). These relationships were independent of age and gender (Table 2, middle).

Results of the multivariable logistic analysis

Multivariable logistic analysis simultaneously adjusted for age, gender, cancer diagnosis, higher serum ALT level, and lower serum sodium level indicated that greater non-opioid analgesic use (adjusted OR: 8.19, 95% CI: 3.37–21.0, P < 0.001), greater opioid analgesic use (adjusted OR: 8.66, 95% CI: 1.99–43.6, P = 0.006) and male gender (adjusted OR: 2.97, 95% CI: 1.24–7.73, P = 0.019) were significantly and independently associated with higher ORs for persistent delirium and that lower serum sodium level was significantly associated with a lower OR (adjusted OR: 0.20, 95% CI: 0.0599–0.543, P = 0.004) (Table 2, right). However, cancer diagnosis (adjusted OR: 1.52, 95% CI: 0.621–3.55, P = 0.347) and higher serum ALT level (adjusted OR: 0.807, 95% CI: 0.314–1.99, P = 0.645) were no longer significantly associated with persistent delirium after the full adjustment (Table 2, right). Moreover, even in models adjusted only for opioid and non-opioid analgesic use, cancer diagnosis was not significantly associated with persistent delirium (adjusted OR: 1.76, 95% CI: 0.756-3.95, P = 0.177).

Pharmacological intervention

The rate of pharmacological intervention did not significantly differ between the nonpersistent and persistent delirium groups. There was no significant difference in the ratio of antipsychotic drug use, ramelteon use, suvorexant use, and trazodone use between the two groups (all P > 0.05, Table 3). Notably, compared with the nonpersistent delirium group, the persistent delirium group was significantly higher ratio of ramelteon or trazodone use (42.0% vs 60.9%, P = 0.022, Table 3).

Discussion

The current study investigated the risk factors for persistent delirium among hospitalized patients of general hospitals that are not limited to a specific situation (e.g., ICU and psychiatric ward). This study showed that both opioid analgesic use and non-opioid analgesic use were significantly and independently associated with persistent delirium in multivariable logistic analysis, even after adjusting for confounding factors including age, gender, non-opioid analgesic use, opioid analgesic use, cancer diagnosis, serum ALT >23 [U/L] and serum Na < 138 [mEq/L].

Past reports on the persistence of delirium include a prospective study of inpatients over 60 years of age in the ICU, in which the persistent delirium group is defined as those inpatients whose delirium continued from their admission to ICU through discharge from the hospital. The study reports that the background factors were age (75 years or older), high doses of opioids (54 mg or more per day in terms of morphine), and use of haloperidol, which were significantly higher in the group of patients with persistent delirium.[16] A report of autopsies of 15 inpatients in a psychiatric unit with critical delirium that lasted until they died showed pathological findings such as Alzheimer's disease in eight cases, Lewy body dementia in three cases, a combination of Alzheimer's disease and Lewy body dementia in two cases, progressive supra-nuclear palsy in one case, and Creutzfeldt-Jakob disease in one case, implying the involvement of neuronal degeneration as their causes.[17] A cohort study of inpatients over 65 years of age and at the sub-acute phase reported that risk factors for delirium continuing 30 days or longer are related to complications of geriatric syndrome, including dehydration, bedsore, pain, astriction, and urinary retention.[23] In addition, a retrospective study of the elderly over 65 years of age following an operation for a fractured hip joint shows a relationship of preoperative dementia as a background factor for delirium continuing for four weeks or longer.[24] In this study, we defined persistent delirium as continuing for 14 days or longer and found that patients with persistent delirium had significantly higher use of analgesics (opioid, non-opioid). This result is consistent with the report by Pisani et al., although the report is restricted to the ICU patients.[16]

Opioid analgesic use is one of the most common causes of delirium among patients with cancer.[25,26] A mechanism involving opioid analgesics controls the effect on a cancer patient via the mu opioid receptor found in the frontal region and limbic cortex, and opioid analgesic inhibits the GABA nerve system, activating the dopamine nerve system of the mesolimbic system and detaching a lot of dopamine from the accumbens nucleus.[27] The results of this study are in accordance with previous reports that the use of opioids is related to persistent delirium, although reported in the situation of ICU.[16] As for non-opioid analgesics, there is a reported case of delirium caused by pregabalin,[28] but, as far as we know, there are no reports of delirium caused by other

non-opioid analgesics. In this study, only one patient in the persistent-delirium group was treated with pregabalin. The relationship between pain and delirium has been pointed out in areas such as palliative treatment and ICU, with an emphasis on assessment and management in these areas.[29,30] In addition, there is a report about elderly patients with dementia who have a fractured hip joint, in which a comparison is made between those elderly whose pain is controlled appropriately and whose pain is not well controlled. The report shows that the latter group had a nine times higher occurrence of complications from delirium, implying that pain is a cause of delirium.[31] It appears that pain is particularly difficult to properly assess in patients with delirium.[29,32] In this study, we did not assess pain; therefore, further study is needed to understand whether analgesics or pain itself affects the persistence of delirium.

Male gender was significantly associated with persistent delirium in the multivariable logistic regression model, although it was not statistically significant in the crude model. Male gender is known to be a preparatory factor for delirium, but there have not been any reports about males as a factor for persistent delirium. It has also been reported that males have a more vulnerable organic brain and less resistance against frailty (i.e., a decline in physiological spare ability due to aging and increased vulnerability to stress).[33] This may be one of the factors contributing to persistent delirium.

Lower serum sodium level (< 138 mEq/L) at the time of admission had a significant association with nonpersistent delirium in the multivariable model. Previous studies have shown a strong association between hyponatremia and delirium among geriatric inpatients.[34,35,36,37] Zieschang et al. investigated the prevalence of delirium due to hyponatremia and the long-term prognosis of patients with hyponatremia.[36] They reported that delirium was diagnosed significantly more often in the hyponatremia group, and among those diagnosed with delirium, the improvement rate of delirium after one week was higher in hyponatremia group. They suggested that delirium associated with hyponatremia might be improved earlier by correcting hyponatremia. We also considered that delirium induced by hyponatremia is likely to be treated relatively quickly by physicians, therefore the duration of delirium was short.

Although cancer diagnoses were significantly associated with persistent delirium in crude logistic regression analysis, it was no longer significant after the full adjustment. In cancer, delirium is the most common neuropsychiatric complication. In the majority of cancer patients, delirium is multifactorial, with a median number of three precipitating factors per delirious episode.[38,39,40] Even if adjusted with only two variables, opioid and non-opioid analgesics use, the relationship between persistent delirium and cancer diagnoses became insignificant. The association between persistent delirium and cancer diagnoses was not an independent association, but we assumed the use of analgesics (probably presence of pain) was a confounding factor. Several studies have shown that etiologies of severe and persistent delirium are explained as

microglial activation caused by inflammation, creating a neurotoxic response and neurodegeneration, [41,42] whereas the present study suggests no relevance between higher serum levels of C-reactive protein (CRP) on admission and persistent delirium.

In this study, 64-74% of patients who developed delirium had received medication. In persistent and nonpersistent delirium groups, 39-50% were receiving ramelteon. Ramelteon is a selective melatonin receptor (MT1 and MT2) agonist, which has the function of adjusting the sleep-wake cycle, and a preventive effect against delirium has been reported.[12,43] The anti-inflammatory effect of ramelteon has been reported as another effect,[44,45] and it is thought that this may act in the prevention of delirium.

Persistent delirium group was significantly higher ratio of ramelteon or trazodone use compared with nonpersistent delirium group, although each use was not significant. It is thought that the medication is being administered because of persistent delirium, but in this study we did not evaluate the effect of the drug. To prevent inappropriate medication or administration of multiple drugs, future cohort studies and intervention studies are necessary to evaluate the effects of the drugs.

Our study has several limitations. First, the targets of this study were limited to patients with delirium seeking psychiatric consultation. The patients, delirium was improved in the short term without being treated by psychiatrists, were excluded. In some cases, appropriate evaluation and medical intervention for delirium were conducted in the general ward. These cases may not necessarily result in intervention from psychiatrists. The treatment of delirium depends on the ward; therefore, further research may be required in terms of which ward the cases come from and the time at which those cases are referred. Further there were 40 cases where delirium had not yet reached 14 days and the patients changed hospitals while they still had delirium symptoms. These patients were excluded from the study, since they were no longer tracked after transferring to another hospital. About half of the patients had dementia. In the case of dementia, it is difficult for patients to return to their home because of nursing-care and rehabilitation problems. In most cases, they are transferred to other hospitals. The cases in which delirium became persistent after changing the hospitals may have affected the results of this study. Consequently, selection bias may have occurred. Therefore, tracking patients after they are transferred to other hospitals should be taken into account. Second, our study did not conduct pain assessment at any stage. Several studies have suggested that untreated pain itself is a risk factor for delirium development.[46,47] Pain assessment should be evaluated in further studies because we need to identify either analgesic use or pain as a risk factor associated with persistent delirium. Third, this is a case-control study and may contain bias. Fourth, the duration of delirium associated with hypoxic causes such as heart failure and respiratory failure generally tends to be prolonged. In this study, however we have not investigated such factors. Fifth, the duration of delirium may be associated with the type of

delirium, such as hypoactive type. However, we have not analyzed the effects of delirium types on persistent delirium.

In conclusion, this study revealed that male gender and the use of analgesics (non-opioid and opioid) were associated with delirium persistence. However, as this is a case-control study and may contain bias, future cohort studies and intervention studies are needed. There is a possibility that pain itself is associated with persistent delirium, it is also necessary to investigate the relevance of the "degree of pain" behind the use of analgesics.

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Disclosure

We have not received any funding for this study. The authors report no conflicts of interest in this study.

Author Contributions

Conception and design of the study: H.G., T.Y., F.Y., M.M., H.U., T.K.; acquisition of data: H.G., T.Y., M.T., H.U., K.K; analysis of data: H.G., T.Y., K.O., K.M.; drafting the manuscript and figures: H.G., T.Y., T.K.; revised manuscript: F.Y., M.M., T.K. All authors reviewed the manuscript and approved for submission.

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Figure legends

Figure 1. Flowchart for diagnosis of persistent delirium and nonpersistent delirium

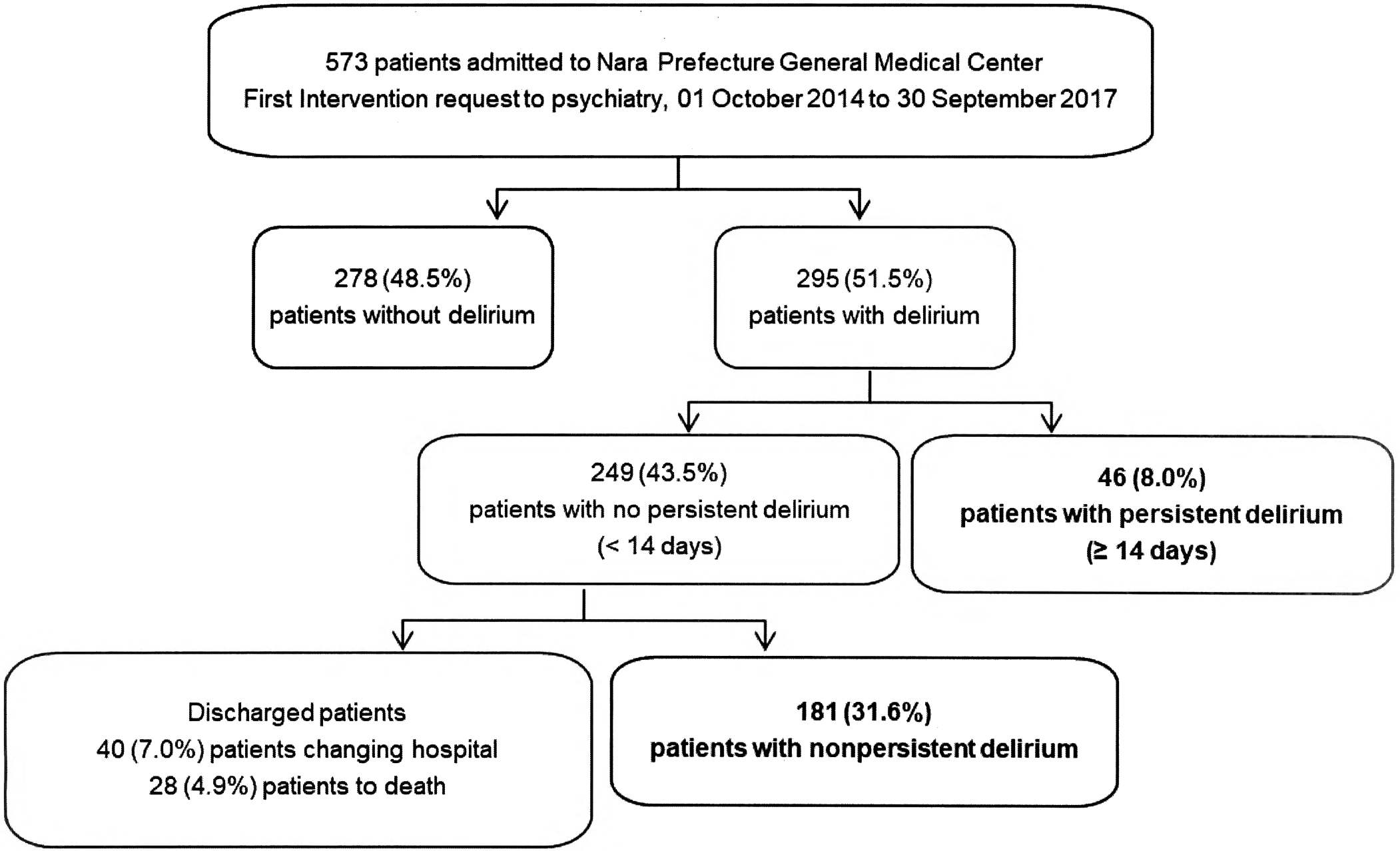
573 patients admitted to Nara Prefecture General Medical Center
First Intervention request to psychiatry, 01 October 2014 to 30 September 2017
278 (48.5%)
patients without delirium
295 (51.5%)
patients with delirium
249 (43.5%)
patients with no persistent delirium
(< 14 days)
46 (8.0%)
patients with persistent delirium
(≥ 14 days)
Discharged patients
40 (7.0%) patients changing hospital
28 (4.9%) patients to death
181 (31.6%)
patients with nonpersistent delirium

Table 1. Basic characteristics and clinical parameters

Characteristics	Nonpersistent delirium (n=181)	Persistent delirium (n=46)	*P* value
Age, mean (SD)	75.8 (11.8)	78.7 (8.0)	0.115
Gender, male, n (%)	109 (60.2)	34 (73.9)	0.122
Dementia, n (%)	53 (29.3)	16 (34.8)	0.586
Habitual alcohol use, n (%)	52 (28.7)	16 (34.8)	0.535
Cancer diagnoses, n (%)	37 (20.4)	20 (43.5)	0.002**
Benzodiazepine use, n (%)	61 (33.7)	18 (39.1)	0.605
Non-opioid analgesic use, n (%)	15 (8.3)	22 (47.8)	<0.001***
Opioid analgesic use, n (%)	5 (2.8)	10 (21.7)	<0.001***
Serum Na, mean (SD)	138.1 (6.1)	140.4 (4.7)	0.015*
Serum Na > 145 [mEq/L], n (%)	10 (5.5)	6 (13.0)	0.145
Serum Na < 138 [mEq/L], n (%)	71 (39.2)	8 (17.4)	0.009**
Serum K [mEq/L], mean (SD)	4.09 (0.76)	4.07 (0.67)	0.888
Serum Ca, mean (SD)	9.13 (0.79)	8.90 (0.74)	0.085
AST [U/L], median (IQR)	28.0 (19.0-50.0)	28.0 (19.3-36.0)	0.481
AST > 30, n(%)	83 (45.9)	18 (39.1)	0.513
AST > 70, n(%)	33 (18.2)	3 (6.5)	0.086
ALT [U/L], median (IQR)	19.0 (13.0-34.0)	15.0 (11.3-21.0)	0.035*
ALT > 23, n (%)	73 (40.3)	10 (21.7)	0.030*
ALT > 100, n (%)	11 (6.1)	1 (2.2)	0.492
CRP [mg/dL], median (IQR)	1.16 (0.23-3.82)	1.29 (0.12-5.60)	0.819
CRP > 1, n (%)	95 (52.5)	24 (52.2)	1.000
CRP > 2, n (%)	77 (42.5)	18 (39.1)	0.780
CRP > 5, n (%)	47 (26.0)	15 (32.6)	0.486
eGFR [mL/min/1.73m^2], mean (SD)	61.3 (34.6)	58.1 (29.8)	0.562
eGFR < 60, n (%)	88 (48.6)	29 (63.0)	0.114
eGFR < 30, n (%)	37 (20.4)	6 (13.0)	0.351

P values for difference between persistent and nonpersistent delirium groups were calculated using an unpaired t-test, the Wilcoxon rank sum test and the chi-squared test. **P* < 0.05. ***P* < 0.01. ****P* < 0.001. SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; AST, aspartate transaminase; ALT, alanine aminotransferase.

Table 2. Odds ratios for persistent delirium

	Crude model		Age/gender-adjusted model†		Final model§	
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.03 (0.995 - 1.06)	0.116	-	-	1.03 (0.991 - 1.07)	0.147
Gender, male	1.87 (0.930 - 3.99)	0.089	-	-	2.97 (1.24 - 7.73)	0.019*
Non-opioid analgesic use	10.1 (4.69 - 22.7)	<0.001***	10.8 (4.84 - 25.4)	<0.001***	8.19 (3.37 - 21.0)	<0.001***
Opioid analgesic use	9.78 (3.27 - 33.0)	<0.001***	9.79 (3.16 - 34.4)	<0.001***	8.66 (1.99 - 43.6)	0.006**
Patients diagnosed with cancer	2.99 (1.50 - 5.95)	0.002**	2.81 (1.39 - 5.68)	0.004**	1.52 (0.621 - 3.55)	0.347
Serum ALT > 23 [U/L]	0.411 (0.183 - 0.852)	0.022**	0.405 (0.176 - 0.866)	0.025*	0.807 (0.314 - 1.99)	0.645
Serum Na < 138 [mEq/L]	0.326 (0.135 - 0.707)	0.007**	0.281 (0.114 - 0.621)	0.003**	0.20 (0.0599 - 0.543)	0.004**

† Adjusted for age and gender. § Adjusted for age, gender, non-opioid analgesic use, opioid analgesic use, patients diagnosed with cancer, serum ALT > 23, and serum Na < 138.

*P < 0.05. **P < 0.01. ***P < 0.001. OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase.

Table 3. Pharmacological intervention

Characteristics	Nonpersistent delirium (n=181)	Persistent delirium (n=46)	*P* value
Pharmacoligical intervention, n (%)	116 (64.1)	34 (73.9)	0.209
Antipsychotics, n (%)	44 (24.3)	12 (26.1)	0.803
Typical antipsychotics, n (%)	5 (2.8)	1 (2.2)	0.824
Atypical antipsychotics, n (%)	39 (21.5)	11 (23.9)	0.730
Ramelteon, n (%)	71 (39.2)	23 (50.0)	0.185
Suvorexant, n (%)	3 (1.7)	0 (0)	0.379
Trazodone, n (%)	20 (11.0)	8 (17.4)	0.243
Ramelteon and trazodone, n (%)	15 (8.3)	3 (6.5)	0.692
Ramelteon or trazodone, n (%)	76 (42.0)	28 (60.9)	0.022*

P values for difference between persistent and nonpersistent delirium groups were calculated using the chi-squared test.

*$P < 0.05$.