【 ORIGINAL ARTICLE 】

Delirium in Patients with COVID-19 in Japan

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Abstract:

Objective   The incidence and clinical importance of delirium in coronavirus disease 2019 (COVID-19) have not yet been fully investigated. The present study reported the prevalence of delirium in patients with COVID-19 and identified the factors associated with delirium and mortality.

Methods   We performed an observational, retrospective study of patients diagnosed with COVID-19 at the Kinki-Chuo Chest Medical Center. Univariate and multivariate logistic regression analyses were used to explore delirium risk factors.

Patients   All consecutive patients diagnosed with COVID-19 at the Kinki-Chuo Chest Medical Center.

Results   We identified 600 patients [median age: 61.0 (interquartile range: 49.0-77.0) years old], of whom 61 (10.2%) developed delirium during their stay. Compared with patients without delirium, these patients were older (median age 84.0 vs. 56.0 years old, p<0.01) and had more comorbidities. Based on a multivariate analysis, age, dementia, severe disease, and lactate dehydrogenase (LDH) levels were independent risk factors for developing delirium. For every 1-year increase in age and 10-IU/L increase in LDH, the delirium risk increased by 10.8-12.0% and 4.6-5.7%, respectively. There were 15 (24.6%) in-hospital deaths in the group with delirium and 8 (1.6%) in the group without delirium (p<0.01). Delirium was associated with an increased mortality.

Conclusion   Delirium in patients with COVID-19 is prevalent and associated with poor clinical outcomes in Japan. Despite difficulties with COVID-19 patient care during the pandemic, physicians should be aware of the risk of delirium and be trained in its optimal management.

Key words: delirium, COVID-19

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [coronavirus disease 2019 (COVID-19)] was confirmed in Wuhan, China, in 2019, and the disease has since spread globally, particularly in older adults (1). Delirium involves impaired consciousness that affects the cerebral-cortical functions and is common in patients with infections. Delirium has been reported to affect 11.0-20.4% of non-severe COVID-19 patients (2-4) and 29.1-54.9% of critically ill patients (5, 6). Delirium in patients with COVID-19 has many possible etiologies, including meta-bolic, respiratory, and cardiovascular alterations due to the effects of SARS-CoV-2 on organs. The reported delirium prevalence in COVID-19 has caried greatly among studies, periods, and countries. Therefore, there is a need for the further exploration of these issues in Japan.

The present study reported the prevalence of delirium during the hospital stay of patients with COVID-19, identified the factors associated with delirium, and evaluated the association between delirium and patients' outcomes. We previously reported on the difference in severity between COVID-19 waves in Osaka Prefecture (7) and now focus on the patients with delirium extracted from this dataset in the present study.

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Materials and Methods

Study subjects

We conducted an observational study on the relationship between several clinical parameters and the severity of delirium in COVID-19 patients at Kinki-Chuo Chest Medical Center, which is a respiratory disease center that was designed to manage patients with mild to moderate COVID-19. All consecutive COVID-19 patients admitted to the hospital between March 1, 2020, and September 30, 2021, were retrospectively assessed.

The diagnosis of COVID-19 was confirmed using polymerase chain reaction tests or antigen tests to detect SARS-CoV-2 in saliva, sputum, or nasopharyngeal swabs. Mild cases were defined as those not requiring oxygen administration, moderate cases as those requiring oxygen administration, and severe cases as those requiring mechanical ventilation, extracorporeal membrane oxygenation, or admittance to the intensive-care unit. Disease severity was defined as the most severe condition recorded during hospitalization. The end of the follow-up period was defined as the discharge date, transfer to an advanced hospital, or death.

Delirium was determined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria or clinical impression, depending on the physician. More than 90% of physicians had participated in the Palliative Care Emphasis Program on Symptom Management and Assessment for Continuous Medical Education (PEACE) program (8), and all nurses had received training in delirium from the Delirium Team Approach (DELTA) program, a systematic management program aimed at screening high-risk groups and preventing delirium (9). Therefore, the diagnosis and management of delirium was well-managed in our institution.

Data collection

The following data were collected: age, sex, disease severity, comorbidities, laboratory data, treatments for COVID-19 and delirium, clinical outcome, and presence of clusters. Comorbidities included hypertension, cardiovascular diseases (coronary heart diseases, cerebrovascular diseases, peripheral arterial diseases, and deep vein thromboses), diabetes, dementia, chronic kidney disease, respiratory diseases, and malignant diseases. Laboratory data upon admission included the white blood cell count, lymphocyte count, C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and ferritin.

This study was approved by the Institutional Review Board at the Kinki-Chuo Chest Medical Center (#795, approval date: 16/JUL/2021).

Statistical analyses

Continuous data were presented as medians [interquartile range (IQR)], and categorical data were presented as frequencies and proportions. We used Wilcoxon's rank sum test for nonparametric continuous variables and Pearson's chi-squared test for categorical variables. Univariate and multivariate logistic regression analyses were used to identify delirium risk factors. Multivariate logistic regression analyses were performed using forced entry, stepwise forward, and stepwise backward methods. All statistical analyses were performed using the Stata/MP software program, version 16.1 (StataCorp, College Station, USA).

Results

Clinical characteristics of COVID-19 patients with delirium

The study population included 600 patients [women: 224; median age: 61.0 (IQR 49.0-77.0)], hospitalized for COVID-19 from April 1, 2020, to September 30, 2021. A total of 61 patients (10.2% of the sample) developed delirium during their hospital stay. Fifty-eight patients (95.1%) developed delirium within the first week of admission, and the remaining 3 patients developed it on days 7-14. Table 1 shows a comparison of clinical characteristics between patients who did and did not develop delirium symptoms.

Patients with delirium were older [median age 84.0 (IQR: 77.5-88.0) vs. 56 (IQR: 49.0-74.0), p<0.01]; had more frequent cardiovascular disease, dementia, and chronic kidney disease (all p<0.01); and more had severe disease symptoms (32.8% vs. 11.3%, p<0.01) than those without delirium. Based on the laboratory data collected on the day of admission, the CRP, D-dimer, and LDH levels were significantly higher in patients who developed delirium than in those who did not (p= 0.013, p<0.01, and p<0.01, respectively).

About half of all patients were on oxygen therapy, and two-thirds of these patients had delirium (Table 2). Patients with delirium often exhibited dyspnea, and morphine was used to treat 14.8% of these patients. The length of stay was significantly longer in delirious patients than in those without delirium [18 days (IQR: 12-23) vs. 11 days (IQR: 10-15), p<0.01]. Mortality was significantly higher in patients who developed delirium during their hospital stay than in those who did not (24.6% vs. 1.6%, p<0.001). Most delirious patients were treated with haloperidol or trazodone or both (Table 3).

Risk factors for delirium

Univariate analysis results showed that severe disease [odds ratio (OR): 5.478; 95% confidence interval (CI): 2.744-10.937; p<0.001], chronic kidney disease (OR: 4.321; 95% CI: 1.836-10.171; p<0.001), dementia (OR: 8.000; 95% CI: 4.031-15.876; p<0.001), age (OR: 1.101 per one-year increase; 95% CI: 1.064-1.140; p<0.01), CRP (OR: 1.063 per unit increase; 95% CI: 1.023-1.105; p<0.01), and LDH (OR: 1.060 per 10-IU/L increase; 95% CI: 1.021-1.110; p<0.01) were significantly associated with delirium development.

Table 1.   Patients' Characteristics on Admission Stratified by Delirium Presence.

	Total (n=600)	delirium+ (n=61)	delirium- (n=539)	p value*
Age, median (IQR)	61.0 (49.0-77.0)	84.0 (77.5-88.0)	56.0 (49.0-74.0)	**<0.01****
Sex, woman (%)	224 (37.3%)	26 (42.6%)	198 (36.7%)	0.40
Infection from clusters	48 (6.3%)	9 (14.8%)	39 (7.2%)	0.04
Smoking history (current or ex-smoker)	186 (31.0%)	24 (39.3%)	162 (30.1%)	0.80
Underlying disease				
Hypertension	206 (34.3%)	24 (39.3%)	182 (33.8%)	0.38
Cardiovascular disease	42 (6.0%)	10 (16.4%)	32 (5.9%)	**<0.01****
Diabetes mellitus	112 (18.7%)	14 (23.0%)	98 (18.2%)	0.36
Dementia	83 (13.8%)	34 (55.8%)	49 (9.1%)	**<0.01****
Chronic kidney disease	33 (5.5%)	10 (16.4%)	23 (4.3%)	**<0.01****
Respiratory disease	108 (18.0%)	12 (19.7%)	96 (17.8%)	0.72
Malignant disease	25 (4.2%)	5 (8.2%)	20 (3.7%)	0.10
Symptoms at admission				
Fever	539 (89.8%)	51 (83.6%)	488 (90.5%)	0.089
Cough	295 (43.3%)	21 (34.4%)	274 (50.8%)	**0.015****
Dyspnea	353 (58.8%)	24 (39.3%)	329 (55.5%)	**0.0011****
Sputum	68 (9.4%)	4 (6.6%)	62 (11.5%)	0.24
Fatigue	247 (41.2%)	13 (21.3%)	234 (43.4%)	**<0.01****
Diarrhea	38 (6.3%)	4 (6.6%)	32 (5.9%)	0.85
Anorexia	106 (17.7%)	11 (18.0%)	95 (17.6%)	0.94
Severity				**<0.01****
Mild	298 (49.7%)	15 (24.6%)	283 (52.5%)	
Moderate	221 (36.8%)	26 (42.6%)	195 (36.2%)	
Severe	81 (13.5%)	20 (32.8%)	61 (11.3%)	
Laboratory data				
WBC (/μL)	5,200 (4,100-6,825)	6,200 (4,000-7,900)	5,000 (4,300-7,200)	0.8
Lymphocyte (/μL)	900 (700-1,200)	900 (600-1,200)	900 (700-1,200)	1.0
CRP (mg/dL)	4.9 (1.8-9.8)	7.6 (3.1-13.4)	4.5 (1.6-8.4)	**0.013****
D-dimer (μg/mL)	1.2 (0.9-1.7)	1.8 (1.2-3.7)	1.0 (0.8-1.4)	**<0.01****
Alb (g/dL)	3.6 (3.3-4.0)	3.0 (2.6-3.4)	3.8 (3.5-4.1)	0.08
AST (IU/L)	38.0 (25.0-58.0)	41.0 (24.0-60.0)	37.0 (27.0-58.0)	0.30
ALT (IU/L)	29.0 (16.0-51.0)	23.0 (15.0-35.0)	27.0 (16.0-52.0)	0.82
LDH (IU/L)	301.0 (227.0-403.0)	416.0 (290.0-468.0)	290.0 (202.0-390.0)	**0.014****
Ferritin (ng/mL)	535.0 (234.3-1,016.2)	729.6 (280.1-1,692.9)	467.1 (220.2-980.5)	0.06

Data are presented as n (%) or median (IQR).

* Pearson's chi-squared test; Wilcoxon's rank sum test.

** p value of <0.05 was considered to be statistically significant. Statistically significant values are indicated in bold.

ALT: alanine aminotransferase, Alb: albumin, AST: aspartate aminotransferase, CRP: C-reactive protein, LDH: lactate dehydrogenase, WBC: white blood cell, IQR: interquartile range

Furthermore, as shown in Table 4, we used three different analysis methods: forced entry, stepwise forward, and stepwise backward. All methods indicated that severe disease (OR: 3.937-4.497), dementia (OR: 5.279-8.046), and age (OR: 1.092-1.120 per 1-year increase) were significantly associated with the development of delirium. The stepwise forward and stepwise backward models identified LDH (OR: 1.046-1.057 per 10-IU/L increase) as significantly associated with developing delirium. In addition, delirium was associated with mortality (OR: 3.476; 95% CI: 1.105-11.900; p= 0.047) in the stepwise forward model.

Discussion

Neurologic manifestations, including delirium, can occur in a broad spectrum of infectious diseases. Previous reports suggested that the coronavirus family is neurotropic (10). Coronaviruses can show neuroinvasive capacity and breach the central nervous system either through the olfactory nerve or via blood circulation and neuronal pathways. After penetrating the blood-brain barrier, SARS-CoV-2 may contribute directly to brain damage by increasing demyelination and interleukin release. In addition to plausible mechanistic pathways, significant environmental factors can explain the occurrence of delirium in SARS-CoV-2 infected patients. Respiratory isolation and restrictions on family visits are standard practices in the hospital management of COVID-19. Despite their importance, measures that limit patient access to caregivers and providers may increase the risk of delirium and delay its diagnosis.

Table 2. Management and Outcome of COVID-19 Patients.

	Total (n=600)	delirium+ (n=61)	delirium- (n=539)	p value*
Oxygen therapy	302 (50.3%)	40 (65.6%)	262 (53.6%)	**0.012****
Mechanical ventilation	58 (9.7%)	8 (13.1%)	50 (10.2%)	0.34
Morphine	11 (2.7%)	9 (14.8%)	2 (0.4%)	**<0.01****
Corticosteroids	370 (61.7%)	35 (61.0%)	335 (68.5%)	0.47
Length of stay (days)	12 (10-16)	18 (12-23)	11 (10-15)	**<0.01****
Death	23 (3.8%)	15 (24.6%)	8 (1.6%)	**<0.01****

Data are presented as the number (%) or median (interquartile range).

* Pearson's chi-squared test; Wilcoxon's rank sum test.

** p value of <0.05 was considered to be statistically significant. Statistically significant values are indicated in bold.

Table 3. Management of Delirium in Patients with COVID-19.

Treatment of delirium	Delirium+ (n=61)
Haloperidol	52 (85.2%)
Trazodone	33 (54.1%)
Quetiapine	8 (13.1%)
Risperidone	2 (3.3%)
Chlorpromazine	1 (1.6%)

Data are presented as n (%).

In the present study, 10.1% of COVID-19 patients developed delirium during their hospital stay. Severe disease was an independent risk factor for delirium development. However, the delirium prevalence in our hospital was lower than in other studies of non-severe cases (2-4). There are important fluctuations in the reported incidence of delirium among different clinical settings and populations of hospitalized patients. In our hospital, high-risk cases of delirium are carefully identified on admission. In addition, preventive measures are taken for high-risk patients (e.g. evaluating delirium risk and precipitating factors; maintaining cognition; sleep promotion; providing adequate nighttime lighting, nutrition, and hydration; and removing access to devices).

In our cohort, 55.8% of patients with delirium had dementia, which is an independent risk factor for delirium. COVID-19-associated pneumonia and hypoxia, as well as direct infection of the central nervous system by SARS-CoV-2, are particularly effective in unmasking the deliriogenic potential of dementia (11). The bidirectional interaction between delirium and dementia has been well-reported by previous studies, as dementia is a risk factor of delirium, but the latter may accelerate subsequent cognitive impairment progression following the acute phase (12, 13). In the present study, most patients with delirium also had dementia, which further increased the risk of poor outcomes. This situation may pose further diagnostic dilemmas, since clinical manifestations of delirium superimposed on dementia are sometimes difficult to distinguish from typical dementia symptoms, especially in clinical contexts where staff lack appropriate training.

According to the multivariate logistic regression analysis,

LDH was an independent risk factor for developing delirium, and for every 10-IU/L increase in LDH, the delirium risk increased by 4.6-5.7%. In a retrospective study including patients hospitalized for COVID-19 in northern Italy, delirium was associated with an increased serum LDH level at admission (2). This fact supports the hypothesis that inflammation mediates the degree of vulnerability to delirium in older people. LDH might be associated with neurocognitive disorders. Another key mechanism of delirium in COVID-19 is the development of secondary encephalopathy, possibly related to cytokine storm. Immune-mediated injury is mainly due to cytokine storm, which increases the levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells (14). Furthermore, these cytokines may damage the blood-brain barrier and induce encephalopathy.

Patients with delirium had a longer hospital stay and a higher mortality rate than those without delirium. In the present study, the mortality rate of COVID-19 patients with delirium was more than 10-fold higher than that of patients without delirium (24.6% vs. 1.6%, p<0.01). Furthermore, patients who ultimately died from COVID-19 had longer hospital stays than patients who survived. Therefore, when mortality cases were excluded, hospital stays for recovered delirious patients were considerably longer than for patients without delirium. The possible additive effect of incident delirium on mortality may also have been masked by the strong association of age and severe COVID-19 clinical presentation with both incident delirium and mortality. Therefore, in older patients with severe COVID-19, preventive measures to avoid the onset of delirium should be encouraged.

Several limitations associated with the present study warrant mention. First, the retrospective design and emergency context of patient care prevented the collection of complete data on delirium subtypes and the timing of the delirium onset. Second, we described a population of mild to moderate patients who were ineligible for intensive care, so caution should be exercised when extrapolating these results to other populations. Third, in the fourth wave (March 1 to June 20, 2021) in Japan, when the number of COVID-19 patients increased rapidly (7), care for delirious patients may have

Table 4. Univariate and Multivariate Analyses of Risk Factors for Delirium.

	Univariate analysis		Multivariate analysis Forced entry		Multivariate analysis Stepwise forward		Multivariate analysis Stepwise backward	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (per 1-unit increase)	1.101 (1.064-1.140)	**<0.001***	1.120 (1.062-1.182)	**<0.001***	1.092 (1.047-1.139)	**<0.001***	1.108 (1.060-1.157)	**<0.001***
Sex (Woman)	0.960 (0.495-1.861)	0.904	0.552 (0.203-1.499)	0.244	-		-	
Severe disease	5.478 (2.744-10.937)	**<0.001***	3.937 (1.281-12.102)	**0.017***	4.419 (1.639-11.918)	**0.003***	4.497 (1.636-12.361)	**0.004***
Underlying disease					-		-	
Hypertension	1.002 (0.606-6.305)	0.827	0.446 (0.332-6.140)	0.546				
Cardiovascular disease	1.074 (0.563-2.049)	0.829	1.177 (0.487-2.846)	0.717	-		-	
Diabetes	1.496 (0.730-3.067)	0.271	1.461 (0.554-3.858)	0.444	-		-	
Dementia	8.000 (4.031-15.876)	**<0.001***	8.046 (2.819-22.961)	**<0.001***	5.279 (2.095-13.305)	**<0.001***	5.864 (2.289-15.020)	**<0.001***
Chronic kidney disease	4.321 (1.836-10.171)	**<0.001***	1.317 (0.354-4.902)	0.682	-		-	
Respiratory disease	1.034 (0.473-2.258)	0.934	0.963 (0.365-2.541)	0.939	-		-	
Malignant disease	1.274 (0.363-4.472)	0.705	1.448 (0.293-7.158)	0.650	-		-	
Laboratory data								
WBC (per 100/µL increase)	1.012 (0.998-1.021)	0.171	1.008 (0.997-1.020)	0.169	-		-	
CRP (per 1-mg/dL increase)	1.063 (1.023-1.105)	**0.002***	1.038 (0.973-1.107)	0.258	-		-	
D-dimer (per 1-µg/mL increase)	1.037 (0.983-1.094)	0.181	1.021 (0.946-1.103)	0.590	-		-	
LDH (per 10-IU/L increase)	1.060 (1.021-1.110)	**0.003***	1.050 (1.000-1.103)	0.051	1.046 (1.011-1.082)	**0.009***	1.057 (1.018-1.098)	**0.004***
Ferritin (per 100-ng/mL increase)	1.032 (1.000-1.088)	0.054	1.023 (0.707-1.070)	0.312	-			
AST (per 10-IU/L increase)	1.018 (0.928-1.117)	0.701	0.946 (0.756-1.184)	0.627	-			
ALT (per 10-IU/L increase)	1.032 (1.000-1.088)	0.230	1.023 (0.707-1.070)	0.371	-			

* p value of <0.05 was considered to be statistically significant.

Statistically significant values are indicated in bold.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, LDH: lactate dehydrogenase, WBC: white blood cell

been inadequate compared with earlier waves. Fourth, the use of systemic corticosteroids was balanced between the delirium group and the non-delirium group; however, about 60% of patients received systemic corticosteroids, which may have exacerbated delirium. Systemic corticosteroids are recommended for COVID-19 patients who require supplemental oxygen (15). Careful attention should be paid concerning the use of systemic corticosteroids in the elderly and/or in a hyper-inflammatory state, which were independent risk factors in the present study.

In conclusion, delirium in patients with COVID-19 is prevalent and associated with poor clinical outcomes in Japan. Physicians should be aware of delirium risk and trained in its optimal management.

The authors state that they have no Conflict of Interest (COI).

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