Original Article

Do the Phenotypes of Symptom Fluctuation Differ Among Motor Subtypes in Patients With Delirium?

Seon-Young Kim, MD, PhD, Jae-Min Kim, MD, PhD, Sung-Wan Kim, MD, PhD, Eun-Song Kim, MD, Hee-Ju Kang, MD, MSc, Ju-Yeon Lee, MD, MSc, Kyung-Yeol Bae, MD, PhD, Il-Seon Shin, MD, PhD, and Jin-Sang Yoon, MD, PhD

Mental Health Clinic Chonnam National University Hwasun Hospital (S.-Y.K., E.-S.K.), Hwasun; Department of Psychiatry (S.-Y.K., J.-M.K., S.-W.K, K.-Y.B., I.-S.S., J.-S.Y.), Chonnam National University Medical School, Gwangju; and Department of Psychiatry (J.-M.K., S.-W.K, H.-J.K., J.-Y.L., K.-Y.B., I.-S.S., J.-S.Y.), Chonnam National University Hospital, Gwangju, Republic of Korea

Abstract

Context. Fluctuation in symptoms is a core feature of delirium. However, it is not well known whether the fluctuating nature would differ or not among the delirium subtype groups.

Objective. This study compared phenotypes of diurnal fluctuation among different delirium subtypes using a prospective design.

Methods. The motor subtypes of delirium patients were determined using the Delirium Motor Subtype Scale, fluctuations in consciousness levels were monitored with the Richmond Agitation-Sedation Scale (RASS), and symptom severity was assessed with the Nursing Delirium Screening Scale (Nu-DESC). All scales were administered at three time points over 24 hours; fluctuations in and phenotypes of symptoms were compared according to subtype of delirium using repeated-measures analysis of variance after adjustment for covariates.

Results. This study included 224 delirium patients. Of this patients, 144 (64.3%) were classified as hyperactive, 25 (11.2%) as hypoactive, 33 (14.7%) as mixed, and 22 (9.9%) as no subtype. Scores on the RASS and Nu-DESC significantly changed during the evening and/or night and there were significant subtype group × time interaction for the RASS and Nu-DESC ($F = 9.66$, $P < 0.001$ and $F = 5.11$, $P < 0.001$, respectively). Post hoc analyses revealed that the hyperactive and mixed subtype groups had higher mean RASS scores and greater ranges of fluctuation than the other groups. The mixed subtype group was differentiated from hyperactive and hypoactive subtype groups by the range of fluctuation in psychomotor activity.

Conclusions. The phenotypes of symptom fluctuation differed among the motor subtypes. These findings further support the rationale that fluctuations are a core feature of delirium and could differentiate delirium subtypes. J Pain Symptom Manage 2018;56:667–677.

Key Words

Delirium, prospective design, subtype, fluctuation, phenotype

Introduction

Delirium is a common neurocognitive disorder characterized by disturbances in attention and cognition that develop over a short period of time and tend to fluctuate in severity throughout the course of a day.[1] The fluctuating nature of symptom severity is a core feature of delirium that distinguishes it from other diagnoses[2,3]; as a result, these fluctuations are included in the diagnostic criteria for delirium.

Delirium can be categorized according to motor subtypes. Lipowski et al.[4] initially described the delirium subtypes as hyperactive and hypoactive, whereas the mixed and neither subtypes were added later.[5] Based on Diagnostic and Statistical Manual of

Address correspondence to: Sung-Wan Kim, MD, PhD, Department of Psychiatry, Chonnam National University Medical School, 160 Baekseoro, Dong-gu, Gwangju 61469, Republic of Korea. E-mail: swkim@chonnam.ac.kr

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Mental Disorders IV-Text Revision (DSM-IV-TR) criteria,[6] several studies have reported differences in symptom phenomenology among these subtypes including variations in perceptual disturbances, thought and mood abnormalities,[7] the expression of several noncognitive features,[8] and symptom severity scores[9] on the Delirium Rating Scale-Revised-98 (DRS-R-98)[10]. Although fluctuations in symptoms are a core feature of delirium and are evident in most delirium patients,[1,7] few studies have investigated differences in fluctuations among the subtypes. Thus, the present study evaluated whether the fluctuating nature of delirium symptoms would differ among the subtypes because a better understanding of this issue could have important clinical value in terms of diagnosis, predicting a diurnal course, the management of symptoms, and educating patients and/or caregivers.

A systemic literature review of electronic databases (PubMed and SCOPUS) produced six papers related to this topic.[7,11–15] Three of these studies did not observe differences in fluctuations on the item score of the DRS-R-98,[11,12,15] whereas another study, which had a large sample size comprising adults ($n = 321$), found that the hypoactive subtype exhibited less fluctuation than the hyperactive and mixed subtypes.[7] All four studies compared the subtypes in terms of a fluctuation item on the DRS-R-98 for which a higher score means a shorter period of fluctuation (hours to minutes). Although differences in period are an important aspect of fluctuation, they do not represent differences in the degree of symptom severity. Furthermore, determining differences in the fluctuating nature of delirium requires serial assessments, but most previous studies did not employ.

We found only two previous studies investigated differences in fluctuation using serial assessments.[13,14] One of these studies reported greater cognitive impairments in the hypoactive subtype compared with the hyperactive subtype, but this study compared only mean differences between the hyperactive and hypoactive subgroups (40 cases met the delirium criteria) and not changes in scores.[13] The other objectively measured behavior over 24 hours using electronic motion analysis and found differences in the amounts of activity exhibited by subjects with the hyperactive and hypoactive subtypes, especially during daytime and evening. This important finding was strengthened by its use of an objective measurement but was limited by its small sample size (30 cases met the delirium criteria) and a narrow focus on motor activity.[14]

Thus, based on previous evidence, we tested the null hypothesis that the phenotypes of symptom fluctuation would not differ by delirium subtype. We compared fluctuations in consciousness and symptom severity among different delirium subtype groups over a 24-hour period using a prospective design.

Method

Study Design and Recruitment

The present study was conducted as one component of a larger parent study designed to evaluate distress and disease course in patients with delirium and their caregivers over 24 hours and after recovery using a prospective cohort design. The subjects were nonpsychiatric inpatients referred to the consultation-liaison psychiatric service of Chonnam National University Hwasun Hospital in South Korea and were consecutively enrolled between July 2011 and May 2013. The inclusion criteria were a diagnosis of delirium according to the DSM-IV-TR,[6] a confirmation provided by two psychiatrists based on results of the Confusion Assessment Method (CAM),[16] care provided by family members who were 18 years of age or older, and fluency in Korean. Patients were excluded from the present study if they exhibited an underlying intellectual disability, dementia, or psychotic disorder; showed communication difficulties (e.g., severe hearing difficulty or deafness, aphasia, mutism, or communication disorders according to the DSM-IV-TR[6]) that existed before the manifestation of delirium; and/or had presented with delirium for more than six months. In addition, patients with delirium who were in the intensive care unit or palliative care ward were excluded from the study.

After being provided with an explanation of the purpose and methodology of the study, all patients or their familial surrogate (depending on the patient's mental status) provided informed consent. In the case of familial surrogate, written informed consent was re-obtained from the patient after recovery from delirium. The study procedure was approved by the Chonnam National University Hwasun Hospital Institutional Review Board.

Demographic and Clinical Characteristics at Baseline

The baseline characteristics assessed in this study included age, sex, and years of education. The doses of benzodiazepine (BZD) receptor agonists, antipsychotics, and opiates during the 24 hours following the baseline measurement (i.e., from 16:00 to 16:00 the next day) were calculated, based on the medication administration. Then, mean equivalent doses (mg/day) of BZD receptor agonists, including BZD and Z-drugs, were converted to an equivalent dose of diazepam,[17] mean equivalent doses of antipsychotics (mg/day) were converted to an equivalent dose of

chlorpromazine,[18] and mean equivalent doses of opiates were converted to an equivalent dose of morphine (mg/day).[19] Scores on the Eastern Cooperative Oncology Group performance status (ECOG-PS) measure, which range from 0 (fully active) to 4 (completely disabled), were assessed to determine the physical status of each patient.[20] ECOG-PS was reported good concordance with other functional scale in patients with advanced medical diseases.[21]

Delirium Duration, Motor Subtype, and Baseline Severity

The duration from delirium detection to consultation was defined based on a review of the clinical medical records of each patient. Delirium motor subtype was determined using the Delirium Motor Subtype Scale (DMSS),[22] which includes 11 items that assess the motor behaviors of delirium patients over the previous 24 hours and classifies patients as hyperactive, hypoactive, mixed, or no subtype.[22] Based on behavior in the previous 24 hours, the hyperactive subtype was classified by increased motor activity, a loss of control, restlessness, and/or wandering; the hypoactive subtype was classified by decreased motor activity, reduced speed of action, lowered awareness, attenuations in the amount or speed of speech, listlessness, and/or reduced alertness; the mixed subtype was classified according to the presence of symptoms from both former subtypes; and no subtype was classified by the lack of symptoms from either subtype. Baseline severity of delirium was assessed with the Korean version of the DRS-R-98 (DRS-R98-K),[10,23] which comprises 13 severity items and three diagnostic items that are rated using a Likert scale.[10] The total severity score ranges from 0 to 39, and a higher score denotes greater severity of delirium. All baseline scales were assessed between 16:00 and 00:00.

Monitoring Fluctuations in Delirium Symptoms

The Richmond Agitation-Sedation Scale[24] (RASS) and the Nursing Delirium Screening Scale[25] (Nu-DESC) were performed by a psychiatrist at three different time points over the course of 24 hours: 16:00−00:00 (evening), 00:00−08:00 (night), and 08:00−16:00 (daytime). The time intervals were referenced according to the Nu-DESC.[25]

The RASS is a 10-point scale ranging from −5 (unarousable) to 0 (calm) to +4 (combative) that has established reliability and validity for rating consciousness.[24] The Nu-DESC is a five-item scale that assesses disorientation, inappropriate behavior, inappropriate communication, illusion/hallucination, and psychomotor retardation; each of the items is scored from 0 to 2, and thus, the range of the total score is 0−10. The Nu-DESC has been validated for screening but also shows promise as a research tool for monitoring the course and severity of delirium.[25] In the present study, changes in RASS score (fluctuations in consciousness), total score on the Nu-DESC (fluctuations in severity), and subscores on the Nu-DESC items (detailed data on fluctuations in symptoms) were used as dependent variables. The baseline RASS and Nu-DESC scales were assessed between 16:00 and 00:00, simultaneously with other scales.

Statistical Analysis

The participants were categorized into four groups based on motor subtype of delirium. The baseline characteristics of the participants were compared using Chi-square (χ^2) tests for categorical variables and analysis of variance (ANOVA) tests for continuous variables, whereas the changes in symptoms over time were assessed by paired *t*-tests in each subtype group. A repeated-measures ANOVA (RMANOVA) was conducted to assess differences in the RASS and Nu-DESC scores based on the interaction effects for time × subtype group after adjusting for all independent variables and baseline RASS and Nu-DESC scores, respectively. In subanalysis, to evaluate fluctuations in symptoms, the five items on the Nu-DESC were analyzed with an RMANOVA, respectively. The confidence intervals in each RMANOVA were adjusted with a Bonferroni correction. Post hoc Scheffé's tests were conducted to assess mean differences and delta (absolute value of score changes) values. *P*-values < 0.05 were considered to indicate statistical significance, and all statistical tests were performed using SPSS, version 21.0 (SPSS, Chicago, IL).

Results

Sample Recruitment

During the recruitment period, 784 consecutive patients who were referred to our Psychiatric Services Department were diagnosed with delirium. Of these patients, 382 were eligible for the study and 224 (58.6%) agreed to participate (Figure 1).

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the patients at baseline are shown in Table 1; the mean (standard deviation [SD]) age was 69.3 (10.6) years, 68 participants (30.4%) were female, and the mean (SD) DRS-R98-K severity score was 17.2 (5.9). In terms of delirium subtype, there were 144 (64.3%) hyperactive participants, 25 (11.2%) hypoactive participants, 33 (14.7%) mixed participants, and 22 (9.8%) no subtype participants. The baseline characteristics did not significantly differ among the delirium subtype groups except for sex and DRS-

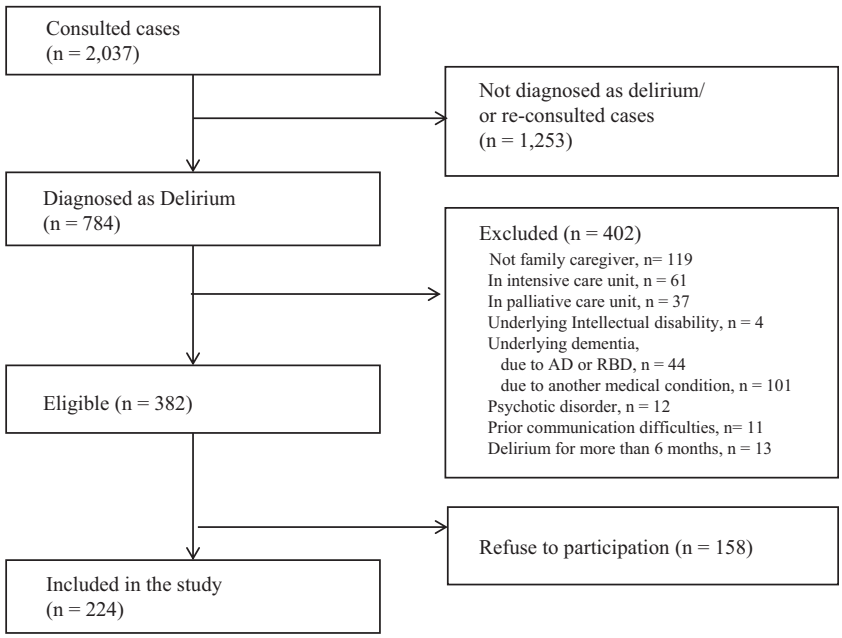

Fig. 1. Flow diagram of baseline recruitment. AD = Alzheimer disease; RBD = dementia with Lewy bodies.

R98-K severity score; female patients were more likely to be classified as the hyperactive delirium subtype, and DRS-R98-K severity was lower in the no subtype group compared with the other subtype groups in post hoc analysis.

Changes in Symptoms Over Time for Each Delirium Subtype

The paired *t*-test results of the RASS and Nu-DESC scores are summarized in Table 2; scores on both the RASS and Nu-DESC significantly changed from evening to nighttime and from night to daytime for the hyperactive subtype group, whereas the scores of the hypoactive subtype group did not significantly change, except for the Nu-DESC scores from evening to night. Changes in the RASS and Nu-DESC scores were significantly different only from night to daytime in the mixed subtype group, whereas the no subtype group significantly differed from evening to night.

Differences in the Characteristics of Changes in RASS and Nu-DESC Total Scores According to Subtypes

The results of the RMANOVA are summarized in Table 3 and Figure 2. Because sphericity was not assumed as indicated by Mauchly's test ($\chi^2 = 46.88$, $P < 0.001$ for the RASS; $\chi^2 = 57.54$, $P < 0.001$ for

Table 1
Baseline Clinical and Sociodemographic Characteristics Among the Delirium Subtypes

	Total ($n = 224$)	Hyperactive ($n = 144$)	Hypoactive ($n = 25$)	Mixed ($n = 33$)	No Subtype ($n = 22$)	Statistical coefficient[a]
Age, mean (SD), yrs	69.3 (10.6)	69.9 (10.5)	70.0 (11.5)	69.8 (8.5)	64.0 (12.5)	$F = 2.10$
Sex, female, n (%)	68 (30.4)	34 (50.0)	14 (20.6)	8 (11.8)	12 (17.6)	$\chi^2 = 15.55$[b]
Years of education, mean (SD), yrs	7.79 (4.3)	7.7 (4.3)	7.4 (4.6)	8.1 (3.6)	8.4 (4.7)	$F = 0.29$
Antipsychotics[c], mean (SD), mg/day	32.9 (84.8)	37.8 (82.3)	10.1 (29.6)	17.9 (38.9)	49.4 (159.9)	$F = 1.39$
BZD-RA[d], mean (SD), mg/day	5.1 (11.1)	6.3 (12.8)	1.9 (4.6)	4.0 (7.3)	3.0 (7.0)	$F = 1.61$
Opiates[e], mean (SD), mg/day	41.6 (89.3)	41.1 (90.5)	27.7 (47.0)	56.0 (126.3)	39.2 (37.3)	$F = 0.49$
ECOG-PS, mean (SD) score	2.64 (0.9)	2.7 (0.9)	2.6 (0.9)	2.7 (0.9)	2.4 (0.9)	$F = 0.80$
Duration[f], mean (SD), days	4.02 (6.8)	4.5 (7.6)	2.6 (2.5)	4.2 (7.0)	2.2 (2.7)	$F = 1.13$
DRS-R98-K severity score, mean (SD) score	17.2 (5.9)	18.0 (5.6)	16.0 (5.0)	18.7 (4.7)	10.9 (6.4)	$F = 12.07$[b]

BZD-RA = benzodiazepines receptor agonist; DRS-R98-K = Delirium Rating Scale-R98-K; ECOG-PS = Eastern Cooperative Oncology Group−performance status; SD = standard deviation.
[a]By χ^2 or ANOVA, as appropriately.
[b]$P < 0.05$.
[c]Conversion of antipsychotic doses to antipsychotic equivalent doses was based on previous research[18]; 100 mg of chlorpromazine was considered equivalent to 1.84 mg of haloperidol, 4.75 mg of olanzapine, 142 mg of quetiapine, and 1.32 mg of risperidone.
[d]Conversion of benzodiazepine doses to diazepam equivalent doses was based on previous research[17]; 10 mg of diazepam was considered equivalent to 0.5 mg of alprazolam, 5 mg of bromazepam, 0.5 mg of clonazepam, 1 mg of flunitrazepam, 1 mg of lorazepam, 3 mg of midazolam, 0.5 mg of triazolam, and 20 mg of zolpidem.
[e]Conversion of opiate doses to antipsychotic equivalent doses was based on previous research[19]; 10 mg of morphine was considered equivalent to 200 mg of codeine, 0.1 mg of fentanyl, 7.5 mg of oral hydromorphone, and 15 mg of oral oxycodone.
[f]Duration of delirium detection to consultation.

Table 2
Paired *t*-Test Results for Each Delirium Subtype According to Time ($n = 224$)

	RASS				Nu-DESC			
	Evening to night[a]		Night to daytime[a]		Evening to night[a]		Night to Daytime[a]	
Subtype	*t*	95% CI	*t*	95% CI	*t*	95% CI	*t*	95% CI
Hyperactive	−6.69[b]	−1.12 to −0.61	13.33[b]	1.47 to 1.99	−8.61[b]	−1.90 to −1.19	15.14[b]	2.29 to 2.98
Hypoactive	−0.85	−0.55 to 0.23	0.68	−0.41 to 0.81	−2.10[c]	−1.90 to −0.02	2.37	−0.29 to 2.37
Mixed	−0.83	−0.84 to 0.35	6.93[b]	1.41 to 2.59	−1.88	−1.83 to 0.07	4.75[b]	1.04 to 2.60
No subtype	−2.63[c]	−1.14 to −0.13	2.08	0.00 to 1.18	−2.59[c]	−1.97 to −0.22	1.48	−0.35 to 2.07

CI = confidence interval; Nu-DESC = Nursing Delirium Screening Scale; RASS = Richmond Agitation-Sedation Scale.
[a]Evening, 16:00–00:00; night, 00:00–08:00; and daytime, 08:00–16:00.
[b]$P < 0.001$.
[c]$P < 0.05$.

the Nu-DESC), Greenhouse-Geisser estimates were applied for the analyses of both the RASS and Nu-DESC scores.

For the RASS scores, there was a significant group × time interaction effect ($F = 9.66$, $P < 0.001$, $\eta^2 = 0.12$). Post hoc analysis of the mean differences revealed that the hypoactive subtype group had a significantly lower mean RASS score than the hyperactive, mixed, and no subtype groups. In addition, the no subtype group had a lower mean RASS score than the hyperactive and mixed subtype groups. Post hoc analyses of the delta values revealed that the hypoactive subtype group exhibited fewer changes in the range of fluctuation than the hyperactive and mixed subtype groups and that the no subtype group had fewer changes in fluctuation than the hyperactive and mixed subtype groups.

For the Nu-DESC total scores, there was a significant group × time interaction effect ($F = 5.11$, $P < 0.001$, $\eta^2 = 0.07$). Post hoc analysis of the mean differences revealed that the no subtype group had a lower Nu-DESC score than the other three subtype groups. A post hoc analysis of the delta values showed that there were no significant differences among the delirium subtypes.

Differences in the Characteristics of Changes in Each Nu-DESC Item According to Delirium Subtypes

The results of the RMANOVA tests for each of the Nu-DESC items are summarized in Table 4 and illustrated in Figure 3; this analysis was adjusted as described previously. Because sphericity was not assumed, as indicated by Mauchly's test ($\chi^2 = 58.53$, $P < 0.001$ for disorientation; $\chi^2 = 40.47$, $P < 0.001$ for inappropriate behavior; $\chi^2 = 52.01$, $P < 0.001$ for inappropriate communication; $\chi^2 = 58.57$, $P < 0.001$ for illusion/hallucination; and $\chi^2 = 81.00$, $P < 0.001$ for psychomotor retardation), the Greenhouse-Geisser correction was applied.

There were significant group × time interaction effects for disorientation, inappropriate behavior, inappropriate communication, and psychomotor retardation. Post hoc analyses of the mean differences revealed that the hyperactive and mixed subtype groups had higher scores than the no subtype and/or hypoactive groups on disorientation, inappropriate behavior, and inappropriate communication. In terms of psychomotor retardation, the hypoactive subtype group had the highest mean score of all the subtype groups and the mixed subtype group had a higher mean score than the hyperactive and no subtype groups. Post hoc analyses of the delta values revealed that the hypoactive subtype and no subtype groups exhibited less fluctuation than the hyperactive and mixed subtype groups with regard to inappropriate behavior, and that the mixed subtype group showed more fluctuation than the hyperactive and no subtype groups with regard to psychomotor retardation.

Discussion

The principal findings of this study were that delirium symptoms significantly changed over time in all four subtype groups. The nature of the fluctuations based on RASS and Nu-DESC scores showed time × subtype group interactions, that is, there were significant differences in the mean RASS and Nu-DESC scores and significantly different ranges of fluctuation in the RASS score among subtypes over 24 hours. Therefore, the null hypothesis that the phenotypes of the fluctuations do not differ among subtypes can be rejected.

Fluctuations Over Time

Analyses of the RASS scores over time revealed elevations in psychomotor agitation during the evening and/or nighttime for all subtypes except the hypoactive group. Similarly, analyses of the Nu-DESC total scores over time showed that the severity levels of delirium symptoms increased during the evening and/or nighttime for all subtypes. This phenomenon is consistent with previous reports of the nocturnal aggravation of delirium symptoms, which could be related to the melatonin system.[2,26] The observed

Table 3
RASS and Nu-DESC Score Changes and Interactions for Time × Delirium Subtype ($n = 224$)

	Hyperactive ($n = 144$)	Hypoactive ($n = 25$)	Mixed ($n = 33$)	No Subtype ($n = 22$)	Group × time[a]		Post hoc[b]	
					F	P	Mean Difference	Delta[c]
RASS[d], mean (SD)								
Evening	1.41 (1.16)	−0.60 (1.00)	1.73 (1.04)	0.18 (0.96)	9.66	<0.001	Ho[e] < He, Mx, No	Ho < He[e], Mx[f]
Night	2.27 (1.11)	−0.44 (1.26)	1.97 (1.36)	0.82 (1.05)			No < Mx[f], He[e]	No[g] < He, Mx
Daytime	0.54 (1.23)	−0.64 (0.86)	−0.03 (1.16)	0.23 (0.87)				
Nu-DESC[d], mean (SD)								
Evening	4.07 (1.99)	3.56 (2.24)	4.70 (1.90)	1.95 (1.84)	5.11	<0.001	No < He[e], Ho[f], Mx[e]	not significant
Night	5.62 (1.84)	4.52 (2.26)	5.58 (1.80)	3.05 (2.08)				
Daytime	2.98 (1.82)	3.48 (2.33)	3.76 (1.64)	2.18 (1.62)				

He = hyperactive subtype; Ho = hypoactive subtype; Mx = mixed subtype; No = no subtype; Nu-DESC = Nursing Delirium Screening Scale; RASS = Richmond Agitation-Sedation Scale; SD = standard deviation.
[a]Repeated-measures analysis of variance adjusted with baseline RASS or Nu-DESC score, age, sex, year of education, antipsychotics, benzodiazepines receptor agonist, opiates, Eastern Cooperative Oncology Group−performance status, duration delirium detection to consultation, and Delirium Rating Scale-R98-K severity score.
[b]Post hoc by Scheffé's tests.
[c]Absolute value of score changes.
[d]Evening, 16:00−00:00; night, 00:00−08:00; and daytime, 08:00−16:00.
[e]$P < 0.001$.
[f]$P < 0.01$.
[g]$P < 0.05$.

fluctuations in both the RASS and Nu-DESC scores are also congruent with diagnostic criterion B for delirium in the DSM-5. In the DSM-IV-TR, criterion C states that delirium tends to fluctuate during the day but does not provide further description. In the DSM-5, criterion B defines these behaviors as a change from baseline attention and awareness that tend to fluctuate in severity. Thus, the present findings support changing the details of diagnostic criterion B in the DSM-5.

Fluctuations According to Delirium Motor Subtypes

The hyperactive and mixed subtype groups had higher mean scores than the no and hypoactive subtype groups for agitation and the no subtype group for delirium severity. In addition, the hyperactive and mixed subtype groups had greater ranges of fluctuation than the hypoactive and no subtype groups for the RASS score, that is, consciousness level. The hyperactive subtype showed significantly increased RASS and Nu-DESC total scores during nighttime compared with evening and daytime. Meanwhile, the mixed subtype group showed increased RASS and Nu-DESC total scores during both evening and nighttime and then decreased scores during daytime. These results are indicative of a pattern of mixed delirium, which differentiate from hyperactive subtype, which could be explained by previous findings showing that the mixed subtype reflects the most severe delirium.[15,27]

Both the hyperactive and mixed subtype groups showed more disorientation and inappropriate behavior/communication than the no and/or hypoactive subtype groups on each item on the Nu-DESC. Psychomotor retardation appeared to be the best symptom to clearly differentiate the mixed and hyperactive subtype groups because the mean score for psychomotor retardation was higher and exhibited wider fluctuations in the mixed subtype group relative to the hyperactive subtype group. Compared with the hyperactive subtype group, the mixed subtype group was similarly agitated in the evening and nighttime based on RASS score but these symptoms attenuated during the daytime. Compared with the hypoactive subtype group, the mixed subtype group similarly exhibited less agitation during the daytime but more agitated in the evening and nighttime. These patterns of behavior support the DSM-5 diagnostic criteria for mixed levels of activity, that is, individuals "whose activity level rapidly fluctuates."[1] In addition, the present findings support the widely accepted concept of the mixed subtype, which differs from the hyperactive and hypoactive subtypes but shares characteristics with both.[5]

The scores of the hypoactive subtype group on the RASS and Nu-DESC showed little change. This group exhibited a lethargy/drowsy mental status more often than did the other subtype groups based on RASS

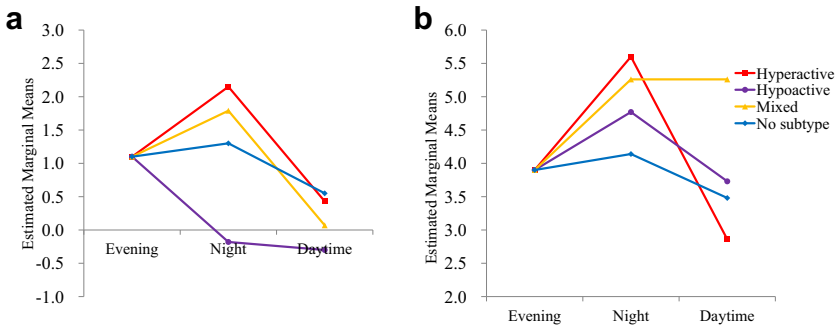

Fig. 2. Changes in baseline scores on the RASS and Nu-DESC over 24 hours ($n = 224$) among the delirium subtypes. a) There was a significant difference in RASS scores for the subtype group × time interaction ($F = 9.66$, $P < 0.001$). b) There was a significant difference in Nu-DESC scores for the significant subtype group × time interaction ($F = 5.11$, $P < 0.001$). Results of a repeated-measures analysis of variance adjusted with baseline RASS or Nu-DESC score, age, sex, year of education, antipsychotic use, benzodiazepine receptor agonist use, opiate use, Eastern Cooperative Oncology Group performance status, duration from delirium detection to consultation, and Delirium Rating Scale-R98-K severity score. Nu-DESC = Nursing Delirium Screening Scale; RASS = Richmond Agitation-Sedation Scale.

scores (<0). Although fluctuations in RASS scores were not significantly observed, the hypoactive subtype group did fluctuate in terms of severity based on the Nu-DESC score. Meanwhile, given that previous research reported that about one in three patients in an intensive care unit had both catatonia and delirium,[28] the minor changes in RASS and Nu-DESC scores in the hypoactive group could be related to catatonia; however, we did not separately analyze or exclude individuals with catatonia. Additional research on the phenotypes involved in the differential diagnosis of delirium and catatonia is needed.

Patients classified in the no subtype delirium group typically report mild forms of delirium.[15,27] Accordingly, the present study found that the baseline DRS-R98-K severity score of the no subtype group was low, which is similar to previous reports.[15,27] Although the mean differences of the no subtype group in RASS and Nu-DESC total scores were lower than those of the hyperactive and mixed subtype groups, the no subtype group also exhibited fluctuations during the day. This finding emphasizes the usefulness of fluctuations as a marker for delirium detection, as previously reported.[27] Serial follow-up assessments of RASS and/or Nu-DESC scores may also aid in the detection of delirium and help with differential diagnoses, even for patients with mild symptom severity. However, in contrast to how the DMSS classifies delirium subtypes, the criterion of "mixed level of activity" in the DSM-5 is defined as an individual with a normal level of psychomotor activity or an individual whose activity level rapidly fluctuates. In contrast, patients with delirium with a normal level of psychomotor activity would be classified as "no subtype" in the DMSS. However, in the present study, the no subtype group clearly differed from the mixed subtype group in terms of severity and the range of symptom fluctuation.

Clinical and Research Implications

Comparing the phenotype of fluctuation would be helpful for differentiating the four delirium subtypes. The accurate identification of delirium subtypes is important because each is associated with a different etiology, management approach, treatment response, pathophysiology, and prognosis.[15,29–33] There have been reports of hypoactive and/or mixed subtypes having shorter survival durations than the other subtypes.[30,34] Although reports are tentative, an anticholinergic etiology is related to the hypoactive subtype,[33] and inverse change in the urine level of 6-sulfatoxymelatonin, which is the chief metabolite of melatonin, between hyperactive and hypoactive subtypes was reported.[31]

The present findings encourage serial follow-up assessments of consciousness level and symptom severity when differential diagnosis of delirium is difficult. Fluctuations in consciousness and severity are core features of delirium, as well as useful markers for delirium detection regardless of subtype.

Finally, elucidation of the different courses of fluctuation among the delirium subtypes will be useful for the management of patients and education of patients/caregivers, and it helps in the prediction of symptom exacerbations.

Strength and Limitations

The present study has several strengths. First, the prospective monitoring of symptom fluctuations overcame limitations encountered by previous studies using cross-sectional designs and/or fragmented aspects of fluctuation. In addition, delirium subtypes were defined using a validated instrument, the DMSS, which improved the accuracy of subtype classification.[35] Furthermore, the present analyses were

Table 4

Changes in Nu-DESC Subscores and Interactions by Time × Delirium Subtype ($n = 224$)

					Group × Time[a]		Post hoc[b]	
	Hyperactive ($n = 144$)	Hypoactive ($n = 25$)	Mixed ($n = 33$)	No Subtype ($n = 22$)	F	P	Mean Difference	Delta[c]
Disorientation[d], mean (SD)								
Evening	1.27 (0.50)	1.12 (0.73)	1.45 (0.51)	0.64 (0.66)	4.90	<0.001	No < He[e], Ho[f], Mx[e]	not significant
Night	1.68 (0.47)	1.32 (0.63)	1.70 (0.47)	0.86 (0.64)				
Daytime	1.01 (0.57)	1.08 (0.70)	1.15 (0.36)	0.77 (0.61)				
Inappropriate behavior[d], mean (SD)								
Evening	0.98 (0.71)	0.20 (0.50)	1.09 (0.68)	0.27 (0.55)	6.57	<0.001	Ho, No < He[e], Mx[e]	Ho[e], No[g] < He, Mx
Night	1.51 (0.68)	0.52 (0.77)	1.42 (0.75)	0.59 (0.80)				
Daytime	0.56 (0.67)	0.28 (0.54)	0.42 (0.66)	0.32 (0.65)				
Inappropriate communication[d], mean (SD)								
Evening	1.15 (0.57)	0.80 (0.71)	1.30 (0.59)	0.73 (0.70)	2.86	0.016	Ho[g], No[f]< He, Mx	not significant
Night	1.56 (0.59)	1.08 (0.70)	1.55 (0.62)	1.00 (0.69)				
Daytime	0.85 (0.57)	0.84 (0.69)	0.91 (0.63)	0.64 (0.73)				
Illusion/hallucination[d], mean (SD)								
Evening	0.49 (0.73)	0.32 (0.63)	0.33 (0.60)	0.18 (0.39)	1.56	0.173	not significant	not significant
Night	0.70 (0.84)	0.44 (0.82)	0.52 (0.67)	0.45 (0.74)				
Daytime	0.22 (0.48)	0.28 (0.61)	0.12 (0.33)	0.23 (0.53)				
Psychomotor retardation[d], mean (SD)								
Evening	0.17 (0.43)	1.12 (0.83)	0.52 (0.51)	0.14 (0.35)	6.62	<0.001	He[e], Mx[g], No[e] < Ho	He[f], No[g] < Mx
Night	0.17 (0.47)	1.16 (0.80)	0.39 (0.50)	0.14 (0.35)			He[e], No[f] < Mx	
Daytime	0.35 (0.64)	1.00 (0.82)	1.15 (0.57)	0.23 (0.43)				

He = hyperactive subtype; Ho = hypoactive subtype; Mx = mixed subtype; No = no subtype; Nu-DESC = Nursing Delirium Screening Scale; SD = standard deviation.

[a]Repeated-measures analysis of variance adjusted with each baseline subscore of Nu-DESC, respectively, age, sex, year of education, antipsychotics, benzodiazepines receptor agonist, opiates, Eastern Cooperative Oncology Group performance status, duration delirium detection to consultation, and Delirium Rating Scale-R98-K severity score.

[b]Post hoc by Scheffé's tests.

[c]Absolute value of score changes.

[d]Evening, 16:00−00:00; night, 00:00−08:00; and daytime, 08:00−16:00.

[e]$P < 0.001$.

[f]$P < 0.01$.

[g]$P < 0.05$.

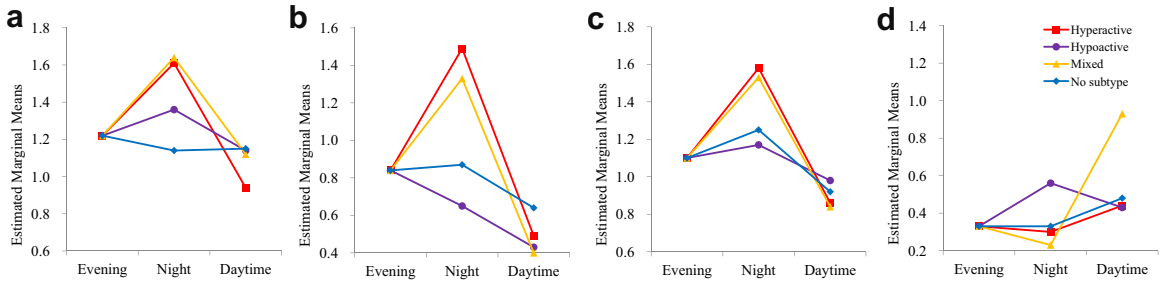

Fig. 3. Changes from baseline on subscores of the Nu-DESC over 24 hours ($n = 224$) among the delirium subtypes. Among 5 items, only the items that show significant subtype × time interaction ($P < 0.05$) on RMANOVA were demonstrated. a) Disorientation; b) inappropriate behaviour; c) inappropriate communication; and d) psychomotor retardation. Results of an RMANOVA adjusted with each baseline subscore of Nu-DESC, respectively, age, sex, year of education, antipsychotic use, benzodiazepine receptor agonist use, opiate use, Eastern Cooperative Oncology Group performance status, duration from delirium detection to consultation, and Delirium Rating Scale-R98-K severity score. Nu-DESC = Nursing Delirium Screening Scale; RMANOVA = repeated-measures analysis of variance.

adjusted for the equivalent doses of BZD, antipsychotics, and opiates, which is important because these drugs can influence sedation, agitation, and hypokinesia.[15,36–38] However, our results are also limited in this regard because we included only medications administered during the 24 hours since the baseline measurement; thus, medications used before baseline were not considered despite their possible effect on baseline delirium symptoms. Moreover, differences in the half-life of each medication were not considered, and we did not adjust for differences in the timing of follow-up doses, as only the summated doses for the first 24 hours were adjusted.

Other several limitations should be considered when interpreting the present results. First, the recruitment of participants from only a single institution may limit the generalizability of the findings. Also, the sample consisted of patients who were referred to a consultation-liaison psychiatric service; thus, the results do not represent the entire population of delirium patients and may be biased by the use of referrals to build our sample. Indeed, previous research has reported that some subtypes of delirium, such as the hypoactive subtype, were referred and assessed less often.[39] Second, the period of fluctuation is defined as "during the course of a day" in the DSM-5,[1] but future studies utilizing longer follow-up periods will be necessary. Third, based on the Nu-DESC, we analyzed data in terms of ordinal time (i.e., units of 24 hours) rather than natural time. The Nu-DESC divides each 24-hour period into three segments according to nursing shifts.[25] Fourth, these results only reflect detectable changes in consciousness (RASS) and severity (Nu-DESC) and do not represent all aspects of the clinical fluctuations of delirium symptoms. Fifth, although the confidence intervals in the RMANOVA were adjusted by the Bonferroni correction using SPSS, the issue of multiple comparisons remains. Sixth, the Nu-DESC was used because it is suitable for the performance of serial assessments during a short period of time (i.e., it is fast and simple to apply). Although the Nu-DESC is a promising tool for monitoring and rating the severity of symptoms, it has been validated only for screening. Future research should include serial assessments with other instruments (e.g., the DRS-R-98) to produce more precise and complete data. Finally, our research design did not account for differences between clinical and research settings. Although we adjusted for the effects of certain medications, many other factors, such as adverse reactions to other drugs, blood transfusions, diarrhea, and dysuria, may influence fluctuations in RASS and Nu-DESC scores in clinical situations.

In conclusion, the present study found that symptom fluctuation was a core feature of delirium, and that the patterns of fluctuations differed among delirium subtypes in terms of time course, severity, and range of changes during a day. These differences in fluctuation phenotypes could be helpful for the screening, differential diagnosis, prediction, and management of delirium.

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