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Clinical Features of Delirium among Patients in the Intensive Care Unit According to Motor Subtype Classification: A Retrospective Longitudinal Study

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Purpose: Delirium in the intensive care unit (ICU) poses a significant safety and socioeconomic burden to patients and caregivers. However, invasive interventions for managing delirium have severe drawbacks. To reduce unnecessary interventions during ICU hospitalization, we aimed to investigate the features of delirium among ICU patients according to the occurrence of hypoactive symptoms, which are not expected to require invasive intervention.

Materials and Methods: Psychiatrists assessed all patients with delirium in the ICU during hospitalization. Patients were grouped into two groups: a "non-hypoactive" group that experienced the non-hypoactive motor subtype once or more or a "hypoactive only" group that only experienced the hypoactive motor subtype. Clinical variables routinely gathered for clinical management were collected from electronic medical records. Group comparisons and logistic regression analyses were conducted.

Results: The non-hypoactive group had longer and more severe delirium episodes than the hypoactive only group. Although the non-hypoactive group was prescribed more antipsychotics and required restraints longer, the hypoactive only group also received both interventions. In multivariable logistic regression analysis, BUN [odds ratio (OR): 0.993, pH OR: 0.202], sodium (OR: 1.022), RASS score (OR: 1.308) and whether restraints were applied [OR: 1.579 (95% confidence interval 1.194–2.089), $p<0.001$] were significant predictors of hypoactive only group classification.

Conclusion: Managing and predicting delirium patients based on whether patients experienced non-hypoactive delirium may be clinically important. Variables obtained during the initial 48 hours can be used to determine which patients are likely to require invasive interventions.

Key Words: Delirium, intensive care unit, physical restraint, antipsychotics

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INTRODUCTION

Delirium is an acute confusional state caused by multiple potential factors, including acute medical illness, drug use or withdrawal, trauma, or surgery. Delirium is a severe neuropsychiatric syndrome characterized by a fluctuating course, attention deficiencies, and significant disorganization of behavior[1] and is prevalent in the intensive care unit (ICU).[2] ICU delirium is associated with higher mortality risk,[3] longer hospital stays,[4] and poor cognitive outcomes.[5]

Both the severity and presentation of delirium can fluctuate. The disorder can be classified under one of four motor subtypes (hyperactive, hypoactive, mixed, and no-subtype).[6] Previous studies suggest that the motor subtypes of delirium have important implications for delirium management.[7,8] Although identifying and treating the underlying causes of delirium is essential to its treatment, pharmacological or non-pharmacological interventions, such as physical restraints, are often used to keep patients and their care team safe and to prevent significant treatment interference.[9,10] Owing to accompanying agitation and restlessness, the frequency of interfering with or refusing necessary treatment or falling is high in hyperactive or mixed motor subtypes.[11-13] Therefore, the hyperactive and motor subtypes have a higher frequency of pharmacological treatment.[14] However, pharmacological and non-pharmacological interventions are also frequently used to prevent adverse events in hypoactive motor subtypes.[15] Owing to the limited benefits of pharmacological or non-pharmacological interventions[16] and drawbacks that may increase mortality, falls, and hospitalization length,[17] it would be beneficial to investigate screening variables for determine the appropriateness of applying these interventions effectively and safely.

Psychomotor subtypes of delirium often fluctuate, rather than representing fixed categories. According to previous research, 38%–50% of delirium patients experience a change in the motor subtype.[18,19] To our knowledge, research on clinical characteristics based on experiences with the hyperactive or mixed subtype during hospitalization, despite the longitudinal change in the motor subtype, is scant. To avoid unnecessary intervention, it could be helpful to identify the clinical features of patients who experience only the hypoactive subtype during ICU hospitalization. Additionally, if information on the need for invasive interventions in an effort to avoid the adverse events of delirium during ICU hospitalization in the subsequent period can be obtained based on the results of the initial examination, it will help establish an effective treatment strategy.

In this study, we aimed to investigate the clinical features of patients with delirium by categorizing them based on whether they experienced a non-hypoactive motor subtype (hyperactive or mixed) during their ICU hospitalization. Additionally, we investigated whether the first confirmed test results and treatment information for patients after admission to the ICU affect subsequent experiences of non-hypoactive motor subtypes.

MATERIALS AND METHODS

Design and setting

This retrospective electronic medical record (EMR)-based study was conducted at a 23-bed, mixed ICU at a university hospital in South Korea (Gangnam Severance Hospital) between March 1, 2013, and May 31, 2017. This study was conducted as part of the ongoing ICU Distress and Delirium Management project (IDDM).[20] Since 2012, this project has been implemented in the ICU of Gangnam Severance Hospital to closely monitor and manage distress and delirium among ICU patients. All patients were evaluated daily, from the time of admission to the time of discharge. All assessment results, regarding alertness, pain, anxiety, and medication use, were stored in EMRs. Gangnam Severance Hospital adheres to the Joint Commission International Standards for hospitals concerning admission and management in the ICU.[21] Additionally, we adhered to the clinical practice guidelines for pain, agitation, and delirium.[22]

Participants

A total of 6386 patients hospitalized in the ICU between March 1, 2013, and May 31, 2017 were initially included. We included all patients for initial data collection, despite some having missing data owing to clinical procedures being performed outside the ICU. The exclusion criteria and number of patients excluded from the analysis are presented in Fig. 1. A total of 40 patients who stayed in the ICU for 45 days or more (mean+2 standard deviation of ICU hospitalization for the initial 6396 patients= 45.06 days) were excluded because an exceptionally long ICU stay could significantly and inappropriately affect the analysis. A total of 1066 patients who met the eligible criteria were grouped. The groups included a "non-hypoactive" group that experienced a non-hypoactive motor subtype (hyperactive or mixed) of delirium once or more times and a "hypoactive only" group that only experienced the hypoactive motor subtype (Fig. 1).

Ethical approval

We received ethical approval to conduct the current study from the local Institutional Review Board of Gangnam Severance Hospital, Yonsei University, South Korea (no. 3-2014-0041) because all measurements were obtained during daily routine management. The need for informed consent was waived. All procedures in this study that involved human participants were conducted in compliance with relevant guidelines and regulations (Supplementary Material, only online), including the ethical standards set forth in the Declaration of Helsinki of 1975.

Delirium assessments

Following the IDDM protocol, ICU nurses conducted daily rounds to identify and evaluate delirious patients. The Richmond Agitation–Sedation Scale (RASS) and the Confusion

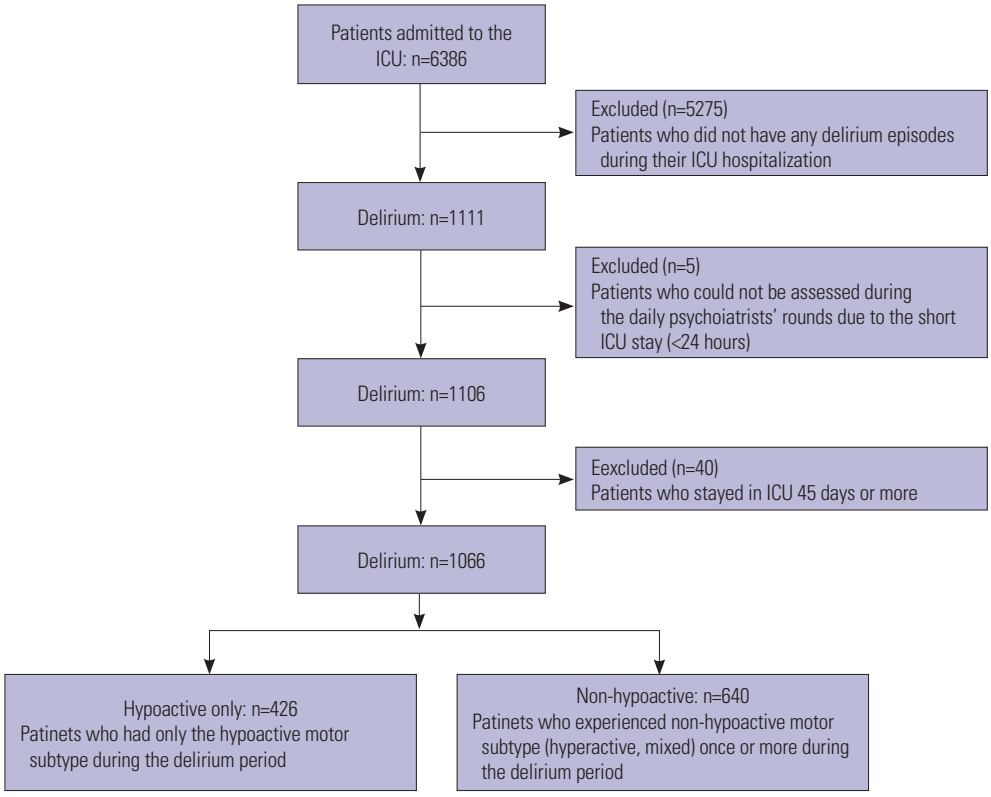

Fig. 1. Study flow chart. Of the 6386 patients enrolled, 426 patients were classified into the hypoactive only group, and 640 patients were classified into the non-hypoactive group. ICU, intensive care unit.

Assessment Method for ICU (CAM-ICU) were used to assess each patient. Trained psychiatrists assessed all of the ICU patients regularly at approximately 10:00 AM for a delirious state based on their medical charts and CAM-ICU results, and determined whether the patients were delirious according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria daily.[1]

When patients were diagnosed with delirium, the severity and motor subtype were assessed by psychiatrists using the Delirium Rating Scale Revised-98 (DRS-R98)[23] and the Delirium Motor Subtype Scale (DMSS).[24] The DMSS is a reliable, validated scale that consists of 11 items (four items for a hyperactive state and seven items for a hypoactive state) based on motor phenotype. The items are rated based on observed motor activity over the previous 24 hours. Items are rated as present or absent. To fulfill subtype criteria, at least two symptoms from the hyperactive or hypoactive list must be present. Individuals who met both the hyperactive and hypoactive requirements were classified under the mixed subtype. Patients who did not meet the criteria for either the hyperactive or the hypoactive motor subtypes were classified as no subtype. Psychiatrists evaluated the DMSS based on medical records, including RASS, interviews with ICU nurses, and patient status at the assessment. The DRS-R98, 16-item clinician-rated scale, including 13 severity items and three diagnostic items, is measured on a four-point Likert scale [range=0 (no severity) to 39 (maximum severity)]. A score of ≥18 points supports a diagnosis of delirium. It is intended to rate symptoms during the past 24 hours. This study used only the 13 severity items of the DRS-R98. RASS was used to assess the agitation or sedation level of patients. RASS is a 10-point scale with four levels of anxiety or agitation (+1 to +4), one level of a calm and alert state (0), and five levels of sedation (-1 to -5).[25]

Clinical data collection

For all patients, sociodemographic data (age, sex) and EMRs, including the durations of ICU hospitalization and delirium, were collected. The duration of delirium was calculated by adding all days each patient was evaluated as having delirium while in the ICU. Additionally, Acute Physiology and Chronic Health Evaluation (APACHE) II scores [range=0 (no acute health problems) to 70 (severe acute health problems)] were computed based on the most abnormal indicators within the first 24 hours after ICU admission.[26] The various medication doses were totaled for each day, and dose equivalents were calculated as chlorpromazine equivalents using accepted conversion rates.[27] The duration of use of vascular catheters, urinary catheters, neurosurgical drainage equipment, ventilators, and physical restraints during ICU hospitalization were also recorded.

To evaluate the association of the first collected clinical data with whether a patient would experience the non-hypoactive

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motor subtype of delirium during the entire admission, 19 clinical variables first identified within 48 hours of ICU admission were used. These clinical variables are known to be associated with delirium and are present in the majority of patients. These included laboratory values, vital signs, and information about devices used during the hospitalization assessment [laboratory test results: blood urea nitrogen (BUN),[28] pH,[29] bicarbonate,[29] C-reactive protein,[30] albumin,[31] total bilirubin,[31] sodium,[32] hemoglobin,[33] hematocrit[33]; vital signs:[34] temperature, diastolic blood pressure, systolic blood pressure, heart rate, and respiratory rate; information about used devices:[34] vascular catheter, urinary catheter, neurosurgical drainage tube, restraints, and mechanical ventilator]. Missing values for categorical variables were assigned to their own null category. The mean of each group was used to fill the missing values for continuous variables. Across all cases, there were 69 cases with at least one missing data point.

Statistical methods

Demographic and clinical data are expressed as n (%) and means with standard deviations for categorial and continuous variables, respectively. For group comparison, independent two-sample t-tests were used for continuous variables, and chi-square tests were used for categorical variables. Univariable logistic regression analyses were conducted to assess the predictive value of clinical variables from the initial 48-hour EMR data, which showed significant differences between the non-hypoactive and hypoactive only groups. Multivariable logistic regression analyses, modeling non-hypoactive subtype, were further constructed from bi-directional stepwise selection based on the Akaike information criterion of all factors from the bivariate analyses that reached a significance of 0.1. Statistical analyses were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). Significance was set at $p<0.05$.

RESULTS

According to DMSS ratings among the 1066 patients diagnosed with delirium, 426 (40%) and 640 (60%) were categorized into the hypoactive only and non-hypoactive groups, respectively. Of the 640 patients in the non-hypoactive group, 236 (36.88%) and 268 (41.88%) were diagnosed with the hyperactive motor subtype and mixed subtype, respectively.

Table 1 shows the demographic and clinical characteristics of the entire ICU hospitalization period according to the two groups. There were no significant differences in demographic data (age, sex) between the hypoactive only and non-hypoactive groups. Concerning clinical characteristics, significant differences between the two groups were noted only for delirium episode duration, DRS-R98 total severity score, and antipsychotic-equivalent dose. The duration of delirium in the

Table 1. Participant Demographic and Clinical Characteristics during Their ICU Stay

Variable	Total (n=1066)	Non-hypoactive (n=640)	Hypoactive only (n=426)	*p* value
Age, yr	68.29±15.64	68.20±15.18	68.43±16.33	0.814
Sex				0.725
Male	685 (61.66)	319 (61.11)	366 (62.14)	
Female	426 (38.34)	203 (38.89)	223 (37.86)	
Initial delirium motor subtype				
Hyperactive subtype	236 (22.14)	236 (36.88)		
Hypoactive subtype	562 (52.72)	136 (21.24)	426 (100)	
Mixed subtype	268 (25.14)	268 (41.88)		
Duration of ICU hospitalization, days	10.81±9.18	11.23±9.44	10.18±8.76	0.068
Duration of delirium, days	4.07±4.62	4.65±5.02	3.20±3.77	<0.001
APACHE II score	19.05±7.22	19.07±7.36	19.01±7.02	0.889
DRS-R98 total severity score	19.74±5.53	20.16±5.83	19.11±4.97	0.002
RASS	-0.71±1.52	-1.68±0.82	0.37±1.38	<0.001
Medication and devices				
Antipsychotics (chlorpromazine equivalents, mg)	12.81±63.20	18.55±75.31	4.18±36.82	<0.001
Duration of vascular catheter	8.89±9.25	9.33±9.55	8.23±8.76	0.056
Duration of urinary catheter	9.51±9.27	9.85±9.56	9.00±8.82	0.145
Duration of drainage	0.41±0.69	0.47±0.69	0.32±0.66	<0.001
Duration of restraints	7.15±7.81	8.05±8.31	5.80±6.80	<0.001
Duration of mechanical ventilated	6.38±9.22	6.49±9.51	6.22±8.78	0.646

APACHE II, Acute Physiological and Chronic Health Evaluation II; DRS-R98, Delirium Rating Scale Revised-98; ICU, intensive care unit; RASS, Richmond Agitation-Sedation Scale.
Values are expressed as a mean±standard deviation or number with characteristics; the percentage (%) represents the number of patients with characteristics/total number of patients. The durations of vascular catheter use, urinary catheter use, drainage, restraints, and ventilation are expressed in days.

non-hypoactive group was longer than that of the hypoactive only group (non-hypoactive: 4.65±5.02; hypoactive only: 3.20±3.77, p<0.001). Individuals in the non-hypoactive group presented higher DRS-R98 total severity scores (non-hypoactive: 20.16±5.83; hypoactive only: 19.11±4.97, p=0.002). Regarding medication and devices, patients in the non-hypoactive group were prescribed more antipsychotics based on the chlorpromazine equivalent dose (non-hypoactive: 18.55±75.31; hypoactive only: 4.18±36.82, p<0.001) and endured restraints and drainage longer than those in the hypoactive only group [drainage duration (non-hypoactive: 0.466±0.693, hypoactive only: 0.32±0.66, p<0.001); restraint duration (non-hypoactive: 8.05±8.31, hypoactive only: 5.79±6.79, p<0.001)].

Table 2 shows the variables related to the first records identified during the first 48 hours of ICU hospitalization for all patients and each group. Of the laboratory tests, BUN (non-hypoactive: 28.33±21.86; hypoactive only: 32.06±26.00, p=0.015), pH (non-hypoactive: 7.36±0.11; hypoactive only: 7.38±0.10, p=0.007), and sodium (non-hypoactive: 136.78±6.71; hypoactive only: 135.94±6.80, p=0.031) between the two groups differed significantly. Among the variables associated with vital signs, only temperature (non-hypoactive: 36.90±0.43; hypoactive only: 36.83±0.37, p=0.031) showed a statistical difference between the non-hypoactive group and the hypoactive only group. Non-hypoactive patients with delirium required restraints (non-hypoactive: 65%; hypoactive only: 58%) and drainage (non-hypoactive: 25%; hypoactive only: 16%) significantly more frequently than patients in the hypoactive only group.

Table 2. Clinical Variables from Initial 48-Hour EMR Data in the ICU among Delirium Motor Subtypes

Variable	Total (n=1066)	Non-hypoactive (n=640)	Hypoactive only (n=426)	*p* value
Laboratory test result				
Blood urea nitrogen, mg/dL	29.82±23.66	28.33±21.86	32.06±26.00	0.015
pH (potential of hydrogen)	7.37±0.10	7.36±0.11	7.38±0.10	0.007
Bicarbonate, mmol/L	20.80±4.93	20.75±4.97	20.87±4.88	0.696
C-reactive protein	92.52±76.91	91.05±76.13	94.73±78.10	0.446
Albumin	2.92±0.67	2.93±0.67	2.89±0.67	0.268
Total bilirubin, mg/dL	1.86±4.15	1.89±2.16	1.82±2.22	0.770
Sodium	136.40±6.25	136.78±6.71	135.94±6.80	0.031
Hemoglobin	10.68±2.18	10.71±4.37	10.62±3.81	0.536
Hematocrit, %	31.04±6.74	31.13±6.20	30.91±6.30	0.618
Vitals				
Temperature, °C	36.87±0.50	36.90±0.43	36.83±0.37	0.031
Diastolic blood pressure, mm Hg	65.54±12.64	65.33±13.49	65.85±12.76	0.518
Systolic blood pressure, mmHg	124.80±20.02	125.58±19.60	123.51±20.38	0.097
Heart rate, beats/min	92.66±21.30	93.09±19.84	92.02±20.41	0.427
Respiratory rate, breaths/min	18.97±5.57	19.16±6.17	18.67±5.71	0.152
Information about used devices				
Vascular catheter				0.932
Not applied	278 (0.26)	168 (0.26)	110 (0.26)	
Applied	788 (0.74)	472 (0.74)	316 (0.74)	
Urinary catheter				0.118
Not applied	148 (0.14)	98 (0.15)	50 (0.12)	
Applied	918 (0.86)	542 (0.85)	376 (0.88)	
Drainage				0.001
Not applied	836 (0.78)	480 (0.75)	356 (0.84)	
Applied	230 (0.22)	160 (0.25)	70 (0.16)	
Restraints				0.012
Not applied	403 (0.38)	222 (0.35)	181 (0.42)	
Applied	663 (0.62)	418 (0.65)	245 (0.58)	
Mechanical ventilator				0.662
Not applied	568 (0.53)	345 (0.54)	223 (0.52)	
Applied	498 (0.47)	295 (0.46)	203 (0.48)	

EMR, electrical medical record; ICU, intensive care unit.
Values are expressed as a mean±standard deviation or number with characteristics; the percentage (%) represents the number of patients with characteristics/the total number of patients.

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Table 3. Factors Predictive of the Non-Hypoactive Subtype

Variable	Univariable		Multivariable (stepwise selection)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Blood urea nitrogen	0.993 (0.988–0.999)	0.013	0.993 (0.987–0.999)	0.016
pH (potential of hydrogen)	0.187 (0.054–0.649)	0.008	0.202 (0.050–0.820)	0.025
Sodium	1.022 (1.002–1.042)	0.031	1.022 (1.001–1.044)	0.036
Temperature	1.317 (1.022–1.697)	0.034		
RASS	1.224 (1.146–1.307)	<0.001	1.308 (1.217–1.406)	<0.001
Drainage (applied)	1.695 (1.240–2.317)	0.001		
Restraints (applied)	1.391 (1.081–1.789)	0.010	1.579 (1.194–2.089)	0.001

CI, confidence interval; OR, odds ratio: RASS, Richmond Agitation-Sedation scale, range -5 (deeply sedated) to 4 (highly agitated).

Table 3 shows all of the variables significantly associated with hypoactive only and non-hypoactive groups in the univariate analyses. In multinomial logistic regression analysis, BUN and pH values were significant predictors of a hypoactive only group classification {BUN, odds ratio (OR): 0.993 [95% confidence interval (CI): 0.987–0.999], p=0.016; pH, OR: 0.202 (95% CI: 0.050–0.820), p=0.025}. Additionally, sodium and RASS values, as well as whether restraints were applied, were significant predictors of a non-hypoactive group designation [sodium, OR: 1.022 (95% CI: 1.001–1.044), p=0.036; RASS, OR: 1.308 (95% CI: 1.217–1.406), p<0.001; restraints, OR: 1.579 (95% CI: 1.194–2.089), p<0.001].

DISCUSSION

This is the first study to explore the clinical characteristics of patients with delirium in the ICU by ascertaining whether they experienced hyperactive or mixed subtype delirium in the ICU. Non-hypoactive was more common than hypoactive only (60% vs. 40%, respectively). No no-subtype case was identified. Although previous research has yet to comprehensively evaluate the prevalence and incidence of initial delirium motor types in the ICU, this study is consistent with previous studies in which the hyperactive or mixed subtype was the most common type of delirium in the ICU.[6,35,36] Furthermore, it is unlikely that a hypoactive motor subtype was not detected because psychiatrists conducted daily assessments to evaluate delirium among all patients in this study. Therefore, our results of the composition of delirium motor subtypes are reliable.

Regarding delirium duration and severity, the non-hypoactive group had longer and more severe delirium episodes than the hypoactive only group. Some studies suggest that patients with delirium diagnosed with a mixed or hyperactive subtype have more severe and longer delirium episodes than patients diagnosed with a hypoactive motor subtype.[18,37] This result is inconsistent with previous studies that showed no differences in delirium duration or DRS-R98 total severity scores among the three groups (hyperactive, mixed, and hypoactive).[35,38] In this study, the non-hypoactive group included patients with delirium, re-categorized from the hypoactive motor subtype. The fact that the mean overall RASS score of the non-hypoactive group was significantly lower than that of the hypoactive-only group indicates that the non-hypoactive delirium group included patients who changed from hypoactive delirium to a non-hypoactive motor subtype in this study. Previous studies show that more drowsiness is a risk factor for hyperactive delirium and affects poor outcomes.[39,40] Therefore, this result may also suggest that a change in the delirium motor subtype is associated with longer and more severe delirium episodes.

There were no significant differences in sociodemographic data (age, sex), clinical state severity (APACHE II score), or prognosis (ICU hospitalization duration) between the two groups. This result is consistent with previous studies that reported no difference in the severity of the clinical state or age according to delirium motor subtype.[38] However, it is difficult to generalize these results because other previous studies reported that patients with the hypoactive motor subtype of delirium were older and had a more severe clinical state than patients with other motor subtypes.[13,41] Nonetheless, the results provide valuable insights as they were derived from data for more than a thousand patients over a considerable period.

Comparing delirium management between the two groups, we noted that patients in the non-hypoactive group were prescribed more antipsychotics drugs and endured restraints longer than those in the hypoactive only group. Although antipsychotic drugs and physical restraints have limitations in controlling agitation among patients with delirium, these are still frequently used for patients in the ICU.[42,43] Additionally, physical restraints were applied for several days (5.798±6.795 days) among patients who were never diagnosed with a hyperactive or mixed subtype during ICU hospitalization,. Considering both the risk of physical restraints and motor features of the hypoactive subtype,[10] this result highlights the importance of reducing unnecessary physical restraints among patients with a hypoactive subtype.

Contrastingly, the prevalence of device applications, such as vascular catheters, urinary catheters, and mechanical ventilators, between the two groups did not show a significant difference. This result is contrary to that of previous studies

that reported differences in vascular catheter use among three delirium motor subtypes: an association between the hypoactive motor subtype and prolonged periods of mechanical ventilation in cardiac surgery.[43,44] Because our research includes all medical/surgical patients, direct comparison is difficult. Additionally, the use of vascular and urinary catheters is often essential for patients in the ICU.[4]

Associations between routinely acquired clinical features and delirium groups were explored through univariate logistic regression analysis. The prevalence of drainage requirements and restraint use in the initial 48 hours of ICU hospitalization was associated with the non-hypoactive group. Because drainage and restraints usually induce pain and are independently associated with delirium,[44] this result also suggests that performing drainage and using restraints may induce a non-hypoactive motor state more easily. However, because of the study design, we cannot establish causality. Therefore, there is a need for further research to clarify this issue.

After controlling other variables, we found that increased BUN, sodium, and pH levels were associated with the hypoactive only group. Additionally, RASS scores and the use of restraints were associated with the non-hypoactive group. An agitated state is expected in the hyperactive motor subtype; therefore, our results concerning RASS scores may suggest that patients with high RASS scores may be classified with non-hypoactive delirium. As the dependent variable in regression analysis was delirium motor subtype for the entire period, our results obtained while considering the initial 48 hours as an independent variable should be interpreted with caution. However, the little available research on risk factors for the motor subtypes of delirium in ICU patients comprises only demographic information, such as sex, age, and APACHE-II scores, and lacks laboratory measurements.[7,40,45] Additionally, given that the laboratory variables used in this study are generally obtained from patients admitted to ICU, our results could help with developing risk prediction models targeting pharmacological prophylaxis and management, as well as effective non-pharmacological interventions, and with reducing unnecessary invasive treatments.

Associations between increased BUN, sodium, and pH levels with delirium have been reported in previous studies.[46,47] One recent study reported an association between increased BUN and occurrence of hypoactive delirium.[28] Increased BUN, sodium, and pH may reflect a dehydrated state. Research has demonstrated that a state of dehydration may contribute to the occurrence of delirium through the mechanisms of cerebral hypoperfusion and modification of neurotransmitter levels in the brain.[48] Although research on the distinct pathophysiology and associated risk factors for different delirium subtypes is scant, one possible mechanism may related to chronic skeletal muscle loss observed in critically ill patients. Indeed, BUN levels have been considered a promising biomarker for chronic muscle catabolism:[49,50] Makiguchi, et al.[51] investigated the relationship between low skeletal muscle mass and the development of hypoactive delirium among postoperative oral cancer patients. Therefore, skeletal muscle loss among ICU patients could be reflected in increased BUN levels and may be associated with hypoactive delirium development.

This study has some limitations. First, because our results were based on an observational study, the association between the initial data included in our study and the motor subtypes of delirium remains to be determined. Particularly, the fact that the first identified clinical variables overlap over the entire length of stay should be interpreted with caution. Second, we did not collect information associated with comorbid dementia, probable or possible etiologies, and other known features that differ among delirium motor subtypes,[52,53] which limits the generalizability of our study. Further well-controlled research that includes more comprehensive clinical characteristics is required to replicate our findings and to establish the possibility of applying our findings in real-world practice. Third, information was collected only for the ICU hospitalization period of a single center according to the IDDM protocol, which limits generalizability. Finally, we could not provide information on overall prognosis because mortality-related information was not collected. Mortality could have potentially affected our results, as it could influence the patient's inclusion in the observation duration. Collecting information on mortality through a new protocol will have important clinical implications in the future.

In conclusion, this longitudinal study suggests that patients in a non-hypoactive state of delirium experience more severe and longer delirium episodes, are prescribed more antipsychotic medications, and receive more invasive interventions than patients in a hypoactive only state. However, invasive management to prevent injuries owing to delirium interventions, such as restraints and medications, appear to be frequently used among hypoactive patients. These observations support the concept that predicting which delirium motor subtypes ate associated with a non-hypoactive motor subtype would offer improved management strategies. Altogether, our results suggest that routinely acquired clinical variables hold the potential to be of use in selecting patients who need invasive management techniques, such as restraints. To reduce unnecessary interventions for patients who are unlikely to experience a non-hypoactive state, it is necessary to develop a predictive model with high accuracy using these variables.

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SUPPLEMENTARY MATERIAL

STROBE Statement—Checklist of Items that Should be Included in Reports of Observational Studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	712
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	712
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	712–3
Objectives	3	State specific objectives, including any prespecified hypotheses	712–3
Methods			
Study design	4	Present key elements of study design early in the paper	713
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	713
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	713–5
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	713–5
Bias	9	Describe any efforts to address potential sources of bias	714–5
Study size	10	Explain how the study size was arrived at	713
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	713–5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	715
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	713
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	715–6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	716
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	716–7
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	717
Discussion			
Key results	18	Summarise key results with reference to study objectives	717
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	718
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	718
Generalisability	21	Discuss the generalisability (external validity) of the study results	717–8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	718

An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.