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Original Research Article

Delirium and Associated Factors in a Cohort of Hospitalized Patients With Coronavirus Disease 2019



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Background: *The coronavirus disease 2019 (COVID-19) pandemic dramatically increased the number of patients requiring treatment in an intensive care unit or invasive mechanical ventilation worldwide. Delirium is a well-known neuropsychiatric complication of patients with acute respiratory diseases, representing the most frequent clinical expression of acute brain dysfunction in critically ill patients, especially in those undergoing invasive mechanical ventilation. Among hospitalized patients with COVID-19, delirium incidence ranges from 11% to 80%, depending on the studied population and hospital setting.*

Objective: *To determine risk factors for the development of delirium in hospitalized patients with COVID-19 pneumonia. Methods:* *We retrospectively studied consecutive hospitalized adult (≥ 18 y) patients with confirmed COVID-19 pneumonia from March 15 to July 15, 2020, in a tertiary-care hospital in Mexico City. Delirium was assessed by the attending physician or trained nurse, with either the Confusion Assessment Method for the Intensive Care Unit or the Confusion Assessment Method brief version, according to the appropriate diagnostic tool for each hospital setting. Consultation-liaison psychiatrists and neurologists confirmed all diagnoses. We calculated adjusted hazard ratios (aHR) with 95% confidence interval (CI) using a Cox proportional-hazards regression model. Results:* *We studied 1017 (64.2% men; median age, 54 y; interquartile range 44–64), of whom 166 (16.3%) developed delirium (hyperactive in 75.3%); 78.9% of our delirium cases were detected in patients under invasive mechanical ventilation. The median of days from admission to diagnosis was 14 (interquartile range 8–21) days. Unadjusted mortality rates between delirium and no*

delirium groups were similar (23.3% vs. 24.1; risk ratio 0.962, 95% CI 0.70–1.33). Age (aHR 1.02, 95% CI 1.01–1.04; $P = 0.006$), an initial neutrophil-to-lymphocyte ratio ≥ 9 (aHR 1.81, 95% CI 1.23–2.65; $P = 0.003$), and requirement of invasive mechanical ventilation (aHR 3.39, 95% CI 1.47–7.84; $P = 0.004$) were independent risk factors for in-hospital delirium development. Conclusions: *Delirium is a common in-hospital complication of patients with COVID-19 pneumonia, associated with disease severity; given the extensive number of active COVID-19 cases worldwide, it is essential to detect patients who are most likely to develop delirium during hospitalization. Improving its preventive measures may reduce the risk of the long-term cognitive and functional sequelae associated with this neuropsychiatric complication.*

(Journal of the Academy of Consultation-Liaison Psychiatry 2022; 63:3–13)

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Received March 16, 2021; revised June 10, 2021; accepted June 28, 2021. From the Department of Neurology and Psychiatry (M.G.-G., E. C., S.L.G.-G., M.d.I.Á.V.-M., L.N.T.-Y., S.I.V.-F., O.A.C.-M., O.A. M.F., A.I.J.-Á., C.C.-B., F.D.F.-S.), Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; Stroke, Dementia & Heart Disease Laboratory (A.J.-R.), Western University, London, ON, Canada; ²Emergency Department (J.d.J.V.-M.), Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; ³Center for Biomedical Science (S.I.V.-F.), Feinstein Institute for Medical Research, Manhasset, NY. Send correspondence and reprint requests to Fernando Daniel Flores-Silva, MD, MSc, Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, 15 Vasco de Quiroga Col. Sección XVI Belisario Domínguez, Tlalpan, 14080, CDMX, Mexico; e-mail: ferfs98@gmail.com

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Key words: delirium, cohort study, COVID-19, SARS-CoV-2, coronavirus, hospitalization.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic dramatically increased the number of patients requiring treatment in an intensive care unit (ICU) or invasive mechanical ventilation (IMV) worldwide.^{1,2} Delirium is a well-known neuropsychiatric complication of critically ill patients with acute respiratory diseases.³ Its development is associated with adverse outcomes, including increased morbidity, length of stay (LOS), cost of care, long-term cognitive sequelae, and increased in-hospital mortality.⁴⁻⁷ Delirium represents the most frequent clinical expression of acute brain dysfunction in critically ill patients undergoing prolonged IMV,⁸ with a reported incidence of 31% to 87% in pre-COVID-19 studies.^{6,9} Despite this high frequency and increasing awareness for its detection among medical and nursing personnel, it is still an underrecognized in-hospital complication, especially in older adults with hypoactive delirium.^{8,10} Among hospitalized patients with COVID-19, incidence rates have been reported from 11% to 80%, depending on the studied population and hospital setting.^{11,12} In severe COVID-19, several well-recognized precipitating factors for its development have been identified, including the use of opioids, sedatives, prolonged IMV, immobilization, and social isolation.^{13,14}

Since the initial reports of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clinical presentation, many series have described a myriad of COVID-19-associated central nervous system manifestations.¹⁵⁻¹⁷ There are several hypotheses on how SARS-CoV-2 may cause acute brain dysfunction, including its neuroinvasive potential (hematogenous or retrograde via the olfactory nerves)¹⁸⁻²⁰ and the proinflammatory and prothrombotic state triggered by SARS-CoV-2,²¹⁻²³ all factors which may increase the risk for delirium development.

Despite the number of confirmed COVID-19 cases worldwide, none of the previous studies on delirium investigated if some of the COVID-19-associated neurologic manifestations were associated with its development^{11-14,24-26}; furthermore, studies describing

the incidence and risk factors for developing in-hospital delirium in Latin American countries are lacking. Therefore, the primary objective of this study was to investigate the incidence of in-hospital delirium and risk factors for its development. As secondary objectives, we explored if COVID-19-associated neurologic symptoms were associated with the development of delirium during hospitalization and describe the differences between psychomotor subtypes in a large cohort of patients with laboratory-confirmed COVID-19 pneumonia from Mexico.

METHODS

Study Design, Setting, and Patient Selection

This retrospective cohort study was conducted at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), a tertiary-care hospital in Mexico City converted into a referral center for patients with COVID-19. Since the conversion, standardized COVID-19 diagnostic and care protocols were implemented at our center; owing to the potential risk of viral aerosolization, all patients under IMV were admitted to the ICU or other ICU-adapted areas and treated by critical care specialists, while non-IMV patients were treated in general medical wards by internal medicine physicians. When beds in the ICU or adapted areas were unavailable, patients needing IMV or ICU admission were transferred to other hospitals.² As part of an ongoing longitudinal study of COVID-19-associated neuropsychiatric syndromes in Mexico City, data of all hospitalized patients with confirmed COVID-19 pneumonia were captured by the NeuroINCMNSZ-COVID-19 research team using standardized case report formats and entered into a secure online database derived from electronic medical records used for multiple observational studies.¹⁷ Here, we present the analysis on in-hospital delirium.

We included consecutive adult patients (aged ≥ 18 y) hospitalized from March 15 to July 15, 2020, with a positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction in respiratory specimens

from nasopharyngeal swabs and COVID-19 pneumonia findings on chest computed tomography (CT) scan. For this analysis, we excluded patients with one or multiple negative real-time reverse transcription-polymerase chain reaction tests for SARS-CoV-2; those discharged or transferred to other hospitals during the first 24 hours after admission; patients with delirium reports by the informant before arrival to the emergency department or diagnosed with delirium upon admission; those with incomplete or without any delirium assessments on the electronic medical record; and patients who died within the first 24 hours after admission.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the INCMNSZ Research and Ethics Committees (reference: NER-3497-20-20-1). Signed informed consent was obtained from all patients or next-of-kin on admission as part of an institutional consent for COVID-19-related observational studies.

Delirium Assessment

Delirium in patients undergoing IMV or in the ICU was assessed by the attending critical care physician or trained nurses after weaning from sedation in those with a Richmond Agitation-Sedation Scale score of -3 or greater.²⁷ This was performed at least once a day using the Confusion Assessment Method (CAM) for the ICU.²⁸ In general wards, the attending internist or trained nurses evaluated patients with suspected delirium using the brief version of the CAM.²⁹ Furthermore, patients with delirium were evaluated by experienced consultation-liaison psychiatrists and neurologists who confirmed the diagnosis. Both screening tools are CAM-based and evaluate the following core features: acute onset and fluctuating course (Feature 1), inattention (Feature 2), disorganized thinking (Feature 3), and level of consciousness (Feature 4). A positive assessment requires the presence of Feature 1 and 2 plus either Feature 3 or 4.^{28–30}

Delirium was recorded in the medical records according to the appropriate assessment tool positivity for each setting as either present or absent. Electronic medical and nursing records of our institution also include detailed daily descriptions (at least once a day) of delirium-associated features, such as level of

consciousness, disorientation, psychomotor agitation, sleep-wake cycle disturbances (hypervigilance or excessive sleepiness), refusal to cooperate with medical care (combative), and disorganized or incoherent speech.^{3,7,10} Those data allowed us to re-evaluate each case and clinically classify them by their initial and predominant psychomotor subtype into hyperactive (agitation, combative behavior, or hypervigilance) or hypoactive (decreased level of consciousness or excessive sleepiness without motor symptoms). In the context of COVID-19 pneumonia, patients with changes in the level of arousal, psychomotor agitation, or anxiety related to severe hypoxemia, respiratory failure, or shortness of breath without a fluctuating course (Feature 1) or disorganized thinking (Feature 3) were not considered as a positive case of delirium.

Definitions

At admission, impaired arousal (either reduced or increased) was defined as presenting to the emergency department with changes in the level of arousal and a Glasgow coma score ≤ 13 points, or as new-onset psychomotor agitation evaluated by the attending physician or referred by the informant before or upon arrival, in patients without other delirium features after delirium screening. Obesity was defined as a body mass index ≥ 30 kg/m². According to our laboratory standards, hyponatremia was defined as a serum sodium level < 135 mEq/L, and hypoalbuminemia as a serum albumin level < 3.5 g/dL. A neutrophil-to-lymphocyte ratio (NLR) ≥ 9 was considered severely elevated; this cutoff value was previously reported in our in-hospital population of patients with COVID-19 pneumonia to predict unfavorable outcomes (ICU/IMV requirement, mortality, or neurologic events).^{17,31} The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen was categorized according to the Berlin definition.³² Chest CT scans were performed in all patients and evaluated by radiologists who semi-quantitatively classified the severity of the findings (consolidation/ground-glass opacities) by visual assessment of the total percentage of lung involvement as mild ($< 20\%$), moderate ($20\text{--}50\%$), or severe ($> 50\%$). On admission, disease severity was evaluated using the National Early Warning Score 2,³³ the mortality risk with the 4C Mortality Score,³⁴ and the Sequential Organ Failure Assessment (SOFA) score.³⁵

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Data Collection

Data were extracted from the NeuroINCMNSZ-COVID-19 research team database using a standardized case report format created for this analysis. Data collection included demographic characteristics; comorbidities, including the history of diagnosed cognitive impairment, neurologic, cardiovascular, pulmonary, or autoimmune diseases; presenting COVID-19-associated symptoms; interval in days from symptom onset to presentation; vital signs on admission; and oxygen saturation on room air. Initial laboratory findings included white blood cell count, blood chemistry (creatinine, blood urea nitrogen, lactate dehydrogenase, sodium, and albumin), inflammatory response biomarkers (ferritin, D-dimer, and C-reactive protein), and arterial blood gas analysis; the following reports of in-hospital complications were also collected: treatment-requiring pulmonary bacterial or fungal (suspected or confirmed) coinfection, pulmonary embolism (confirmed by CT angiography), intermittent hemodialysis-requiring acute kidney injury, in-hospital acute stroke, diagnosed by brain CT or magnetic resonance imaging, and new-onset seizures. We also registered the use of vasopressor, opioids, benzodiazepines, propofol, and antipsychotics (ever used) during hospitalization; IMV/ICU requirement and IMV duration; the interval in days from admission to delirium onset; hospital LOS; and outcome. All data were reviewed and collated with the medical records, nursing records, laboratory findings, and radiologic examinations by at least two researchers. A third researcher adjudicated any difference in interpretation between the primary reviewers.

Statistical Analysis

Categorical variables are reported as frequencies and proportions; continuous variables are described as median with interquartile range (IQR) or as mean with standard deviation. Analyses of categorical variables were performed with the χ^2 or Fisher's exact tests, and continuous variables with the Student's *t*-test or Mann-Whitney *U* test, as appropriate. Univariable Cox proportional-hazard regression was used to determine candidate variables associated with a higher risk for developing in-hospital delirium. We constructed multivariable Cox proportional-hazards regression models censored at death or hospital

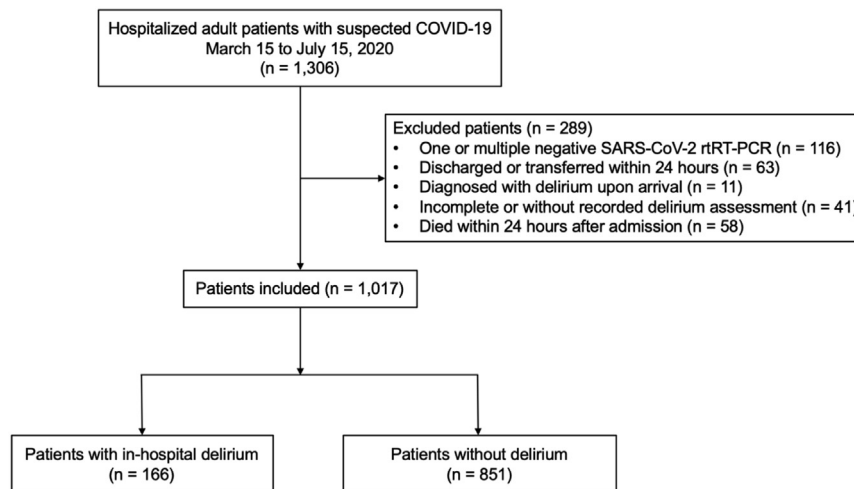
discharge for patients who did not develop delirium; all models were adjusted for candidate-independent covariables based on biological plausibility, including those described in the literature and variables with a *P*-value ≤ 0.2 resulting from the univariable regression analysis. The final model adjustments were made using the following variables, age, sex, pre-existing neurologic disease, pre-existing cognitive impairment, SOFA score at admission, NLR ≥ 9 , C-reactive protein, IMV, in-hospital complications, and use of benzodiazepines, opioids, or propofol. Antipsychotics were not included in these models because all patients received them after the diagnosis was confirmed, therefore not related to delirium development. Further adjustment for other comorbidities, non-neurologic COVID-19-associated symptoms, laboratory findings, and percentage of lung damage by chest CT scan did not affect the estimates reported in the final model, and the results of these adjustments are not presented. We report the final model results as adjusted hazard ratios (aHR) with 95% confidence interval (CI). All values were two-tailed and considered significant when the *P* value was ≤ 0.05 . Statistical analyses were performed with IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY).

RESULTS

During the study period, 1306 patients with suspected COVID-19 were admitted to our center. After evaluation, 289 cases were excluded (Figure 1). We included 1017 cases for the final analysis: 364 women (35.8%) and 653 (64.2%) men, with a median age of 54 (IQR 44–64) years (Table 1). Pre-existing neurologic diseases were reported in 56 (5.5%) cases; the most common were diabetic neuropathy (18/56, 32.1%), epilepsy (13/56, 23.2%), migraine (8/56, 14.3%), stroke (7/56, 12.5%), and history of meningitis (4/56, 7.1%). Pre-existing cognitive impairment was reported in 1.4%.

In 164 (16.3%) patients, delirium was confirmed (98% of those tested positive for a screening tool; 71.1% men; median age, 54 y; IQR, 44–64). The median of days from admission to diagnosis was 14 (IQR, 8–21) days. Comorbidities were similar between groups. Patients who developed delirium presented with dyspnea and muscle pain more often than those without

FIGURE 1. Patients' Selection Flowchart.



Abbreviations: COVID-19 = coronavirus disease 2019; rRT-PCR = real-time reverse transcription–polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

delirium; there were no differences in other presenting neurologic and non-neurologic COVID-19-associated symptoms (Table 1). On admission, patients with delirium exhibited lower oxygen saturation levels and higher breathing rates, as well as lower lymphocyte counts, higher neutrophil counts, and lower albumin levels. Although there were statistical differences in creatinine and blood urea nitrogen levels, both fell within normal limits. C-reactive protein, D-dimer, and lactate dehydrogenase levels were higher in patients with delirium.

At admission, patients who developed in-hospital delirium had lower ratios of the partial pressure of arterial oxygen to the fraction of inspired oxygen (median 140.5, IQR 97.3–205, vs. 206.7, IQR 130–271.9) and higher NLR (median 12.69, IQR 8.58–19.24, vs. 8.26, IQR 5–14.47) and percentage of lung damage on CT scans and severity scores (Table 2 and Supplemental Table 1). These patients also had higher rates of non-neurologic and neurologic in-hospital complications, including new-onset seizures (3.6% vs. 0.2%) and acute stroke (3% vs. 0.2%). Patients with delirium were more likely to be under IMV; also, the duration of IMV and LOS was longer in these patients. The use of sedatives, opioids, or antipsychotics was higher in those who developed delirium. Unadjusted mortality rates between groups were similar (23.3% vs. 24%; risk ratio 0.962, 95% CI 0.70–1.33).

Motric Subtypes of Delirium

Out of 166 patients who developed delirium, 125 (75.3%) cases were classified as hyperactive, and 41 (24.7%) as hypoactive; the latter presented earlier during hospitalization (median 7 d, IQR 2–14, vs. 16 d, IQR 12–22) (Supplemental Table 2). Presenting symptoms, inflammatory response biomarkers, and other laboratory findings were similar. All the characteristics and their differences between delirium motoric subtypes are available in the Supplemental Material. There were no statistical differences in ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, NLR, the proportion of patients with >50% of lung damage by chest CT, or severity scores between groups (Supplemental Table 3). Patients with hypoactive delirium had a higher frequency of pulmonary coinfection, IMV, vasopressor support, longer duration of IMV, and hospital LOS. In contrast, sedatives, opioids, or antipsychotics were more frequently used among patients with hyperactive delirium. There were no differences in other in-hospital complications. Unadjusted mortality was higher in patients with hypoactive delirium (43.9% vs. 17.6%; risk ratio 1.49, 95% CI 1.11–1.99).

Risk Factors for Delirium Development

Multivariable Cox proportional-hazards regression analysis showed that age (aHR 1.02, 95% CI 1.01–1.04;

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TABLE 1. Baseline Characteristics and Initial Biomarkers at Hospital Admission

	Total (n = 1017)	No delirium (n = 851)	Delirium (n = 166)
Male sex, n (%)	653 (64.2)	535 (62.9)	118 (71.1)
Age, median (IQR), y	54 (44–64)	52 (42–62)	54 (44–64)
Comorbidities			
Diabetes, n (%)	278 (27.3)	233 (27.4)	45 (27.1)
Hypertension, n (%)	304 (29.9)	250 (29.4)	54 (32.5)
Pre-existing neurologic disease, n (%)	56 (5.5)	44 (5.2)	12 (7.2)
Pre-existing cognitive impairment, n (%)	14 (1.4)	11 (1.3)	3 (1.8)
Pulmonary disease, n (%)	38 (3.7)	30 (3.5)	8 (4.8)
Smoking, n (%)	150 (14.7)	129 (15.2)	21 (12.7)
Chronic kidney disease, n (%)	22 (2.2)	17 (2)	5 (3)
Cardiovascular disease, n (%)	51 (5)	41 (4.8)	10 (6)
Autoimmune disease, n (%)	61 (6)	51 (6)	10 (6)
Obesity, n (%)	478 (47)	394 (46.3)	84 (50.6)
Presenting symptoms			
Days from symptom onset, median (IQR)	8 (6–10)	8 (6–10)	7 (5–10)
Fever, n (%)	855 (84.1)	715 (84)	140 (84.3)
Headache, n (%)	422 (41.5)	351 (41.2)	71 (42.8)
Anosmia, n (%)	74 (7.3)	63 (7.4)	11 (6.6)
Dysgeusia, n (%)	101 (9.9)	83 (9.8)	18 (10.8)
Diarrhea, n (%)	182 (17.9)	149 (17.5)	33 (19.9)
Dyspnea, n (%)	873 (85.8)	713 (83.8)	160 (96.4)
Muscle pain, n (%)	398 (39.1)	321 (37.7)	77 (46.4)
Impaired arousal, n (%)	25 (2.5)	16 (1.9)	9 (5.4)
Vital signs at presentation			
Mean arterial pressure, mean (\pm SD), mmHg	91 (12)	92 (12)	90 (13)
Heart rate, mean (\pm SD), beats/min	102 (17)	102 (17)	104 (18)
Breathing rate, mean (\pm SD), breaths/min	29 (9)	28 (8)	32 (10)
SpO ₂ on room air, mean (\pm SD), %	78 (14)	79 (13)	72 (16)
Blood workup			
WBC, median (IQR), 10 ⁹ /L	8.2 (5.9–11.4)	8.1 (5.8–10.9)	9.9 (7.1–13.7)
C-reactive protein, median (IQR), mg/dL	15.25 (7.79–23.3)	14.68 (6.72–22.19)	19.31 (12.45–27.19)
Ferritin, median (IQR), ng/dL	623 (319.6–1076)	609.8 (310–1072.8)	683.8 (349–1244)
D-dimer, median (IQR), ng/dL	818 (515–1296)	780 (491–1232)	946 (668–1875)
Lactate dehydrogenase, median (IQR), U/L	377 (291–495)	365 (283–482)	427 (344–557)
Creatinine, median (IQR), mg/dL	0.93 (0.77–1.19)	0.93 (0.76–1.17)	1 (0.81–1.32)
Blood urea nitrogen, median (IQR), mg/dL	16 (11.7–23.9)	15.5 (11.4–22.8)	20.4 (13.6–29.2)
Hyponatremia, n (%), <135 mEq/L	420 (41.3)	352 (41.4)	68 (41)
Hypoalbuminemia, n (%), <3.5 g/dL	394 (38.7)	295 (34.7)	99 (59.6)

Abbreviations: IQR = interquartile range; SD = standard deviation; SpO₂ = oxygen saturation; WBC = white blood cells.

$P = 0.006$), an initial NLR ≥ 9 (aHR 1.81, 95% CI 1.23–2.65; $P = 0.003$), and requirement of IMV (aHR 3.39, 95% CI 1.47–7.84; $P = 0.004$) were independent risk factors for in-hospital delirium development (Table 3). Figure 2 shows the cumulative hazard for delirium development according to hospital setting during hospitalization.

DISCUSSION

To our knowledge, the present cohort is the most extensive single-center study in Latin America describing patients with laboratory-confirmed COVID-19 pneumonia

who developed in-hospital delirium. In this study, including ICU (all under IMV) and non-ICU patients, delirium incidence was 16.3%. The reported incidence in other series of hospitalized patients with COVID-19 ranges from 11% to 80%.^{11,12} Several well-known predisposing (patient characteristics) and precipitating factors (e.g., disease severity, in-hospital setting, in-hospital complications, and the use of sedatives in IMV patients) may explain these differences,³ especially in patients with COVID-19 who are prescribed opioids for symptomatic treatment of dyspnea.^{36,37}

Our incidence is slightly higher than the 11% reported in an Italian retrospective cohort of 852 ICU

TABLE 2. Severity of Disease, In-Hospital Events, and In-Hospital Outcome

	Total (n = 1017)	No delirium (n = 851)	Delirium (n = 166)
Severity of disease			
PaO ₂ /FiO ₂ ratio ≤ 200 mmHg, n (%)	530 (52.1)	407 (47.8)	123 (74.1)
Lung involvement by chest CT > 50%, n (%)	554 (54.5)	425 (49.9)	129 (77.7)
Neutrophil-to-lymphocyte ratio ≥ 9, n (%)	513 (50.4)	391 (45.9)	122 (73.5)
4C Mortality Score, n (%), high to very high risk	524 (51.5)	422 (49.6)	102 (61.4)
NEWS2 score, n (%), high risk	655 (64.4)	537 (63.1)	118 (71.1)
SOFA score, median (IQR)	2 (1–3)	2 (1–3)	3 (2–4)
In-hospital events			
Pulmonary coinfection, n (%)	262 (25.8)	146 (17.2)	116 (69.9)
Pulmonary embolism, n (%)	26 (2.6)	18 (2.1)	8 (4.8)
Hemodialysis-requiring AKI, n (%)	107 (10.5)	64 (7.5)	43 (25.9)
New-onset seizures, n (%)	8 (0.8)	2 (0.2)	6 (3.6)
In-hospital acute stroke, n (%)	7 (0.7)	2 (0.2)	5 (3)
In-hospital medications			
Benzodiazepines, n (%)	222 (21.8)	110 (12.9)	114 (68.7)
Opioids, n (%)	229 (22.5)	117 (13.7)	112 (67.5)
Propofol, n (%)	185 (18.2)	84 (9.9)	101 (60.8)
Antipsychotics, n (%)	70 (6.9)	5 (0.6)	65 (39.2)
Vasopressor support, n (%)	240 (23.6)	115 (13.5)	125 (75.8)
In-hospital outcomes			
IMV, n (%)	247 (24.3)	116 (13.6)	131 (78.9)
Duration of IMV, median (IQR), d	12 (8–17)	8 (4–12)	14 (11–22)
Length of stay in days, median (IQR)	7 (4–13)	6 (4–9)	24 (16–33)
In-hospital death, n (%)	238 (23.4)	198 (23.3)	40 (24.1)

Abbreviations: AKI = acute kidney injury; CT = computed tomography; FiO₂ = fraction of inspired oxygen; IMV = invasive mechanical ventilation; IQR = interquartile range; NEWS2 = National Early Warning Score 2; PaO₂ = arterial partial pressure of oxygen; SOFA = Sequential Organ Failure Assessment.

and non-ICU patients aged ≥ 18 years, with suspected or confirmed COVID-19. In that cohort, patients with delirium were older (median age of 82 y, IQR 78–89) than ours and had higher rates of neurologic and non-neurologic comorbidities than those without delirium; other precipitating factors such as ICU admission or IMV rates were not reported. Contrary to our findings in which mortality rates were similar between groups, they report higher mortality among patients with delirium (57% vs. 30%), but its development was not independently associated with this outcome.¹²

A Brazilian study of 707 ICU and non-ICU patients (aged ≥ 50 y) with probable or confirmed COVID-19 reported an incidence of 24% using a chart-based screening tool.²⁶ Despite this higher incidence, their IMV rates among patients with delirium were lower than ours (53% vs. 78.9%). Some factors that may have contributed to such incidence differences are that their patients were older and had higher rates of pre-existing neurologic diseases (e.g., dementia and cerebrovascular disease) and chronic diseases, well-

known predisposing factors.^{3,38} In contrast to the present series and the Italian cohort, the Brazilian study reported that delirium was independently associated with increased in-hospital mortality (odds ratio 1.75, 95% CI 1.15–2.66; *P* = 0.009); this association was consistent among two different age groups. Similar to our findings, in their population, delirium was associated with IMV (odds ratio 1.99, 95% CI 1.30–3.05; *P* = 0.001) and ICU admission (odds ratio 3.32, 95% CI 2.11–5.23; *P* < 0.001).²⁶

During the pandemic, most studies on delirium have been carried out in ICU patients, reporting an incidence of up to 80%.^{11,13,14} This frequency is much higher than the 31% reported in a pre-COVID-19 meta-analysis of 48 studies.⁹ Of our total sample, 247 (24.3%) patients were treated at the ICU (all under IMV), and 131 of this 247 (53%) developed delirium (78.9% of our delirium cases). A multicenter cohort including 2088 critically ill patients with COVID-19 (71.7% males; median age of 64 y, IQR 54–71) from 69 ICUs across 14 countries reported a delirium

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TABLE 3. Risk Factors for In-Hospital Delirium Development in COVID-19 Pneumonia

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i> value	aHR (95% CI)	<i>P</i> value
Age, y*	1.02 (1.00–1.03)	0.017	1.02 (1.01–1.04)	0.006
Male sex	1.31 (0.93–1.84)	0.12	1.38 (0.96–1.98)	0.085
Pre-existing neurologic disease	1.19 (0.66–2.14)	0.57	1.76 (0.95–3.29)	0.074
Pre-existing cognitive impairment	1.19 (0.38–3.75)	0.762	1.50 (0.43–5.19)	0.521
Anosmia	0.97 (0.53–1.79)	0.923	0.82 (0.31–2.19)	0.692
Dysgeusia	1.15 (0.71–1.88)	0.573	1.62 (0.73–3.58)	0.233
SOFA score*	1.21 (1.10–1.33)	<0.001	1.05 (0.94–1.18)	0.395
NLR \geq 9	2.15 (1.52–3.03)	<0.001	1.81 (1.23–2.65)	0.003
C-reactive protein*	1.02 (1.00–1.03)	0.022	0.99 (0.98–1.01)	0.685
Invasive mechanical ventilation	2.54 (1.68–3.83)	<0.001	3.39 (1.47–7.84)	0.004
Benzodiazepine treatment	2.04 (1.44–2.89)	<0.001	1.07 (0.63–1.81)	0.810
Opioid treatment	1.76 (1.24–2.50)	0.002	0.79 (0.48–1.29)	0.339
Propofol treatment	1.78 (1.28–2.49)	0.001	1.12 (0.73–1.72)	0.606
New-onset seizures	0.87 (0.35–2.16)	0.755	0.86 (0.32–2.35)	0.768
In-hospital acute stroke	0.58 (0.24–1.44)	0.242	0.50 (0.18–1.39)	0.186
Hemodialysis-requiring AKI	1.55 (1.09–2.19)	0.015	1.18 (0.80–1.74)	0.394
Pulmonary coinfection	1.35 (0.93–1.95)	0.117	0.66 (0.42–1.03)	0.066

Abbreviations: aHR = adjusted hazard ratio; AKI = acute kidney injury; CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; SOFA = Sequential Organ Failure Assessment.

* These are continuous variables. Overall model adjustment: $\chi^2 = 59.56$, 17 df, $P < 0.001$.

prevalence of 66.9%, and 87.5% of their patients required IMV at some point during hospitalization. Older age, higher Simplified Acute Physiology Score II scores, male sex, smoking or alcohol abuse, use of vasopressors, IMV, continuous benzodiazepine, and opioid infusions were directly associated with its appearance and duration.¹⁴

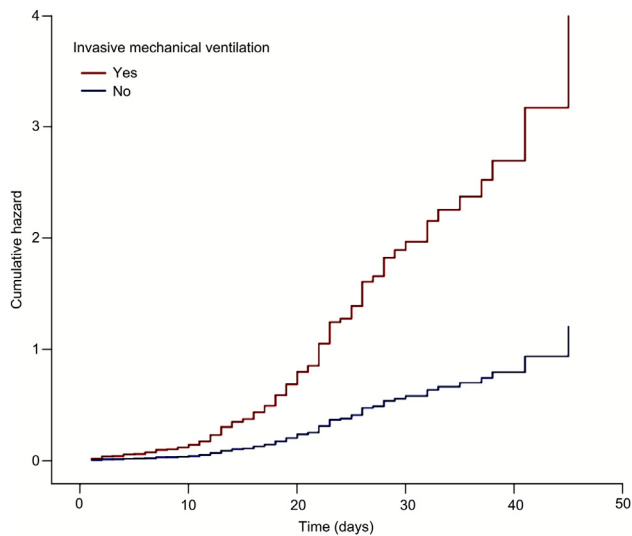
Regarding the motoric subtypes of delirium in patients with COVID-19, to this day, there are no data from non-ICU patients, and incidence among critically ill patients has significant variation. Hypoactive delirium is reported in 41.9% to 87.4% (mean duration of 2–4 d) of cases, and hyperactive in 12.6% to 51.8% (mean duration of 0–2 d).^{11,14} In our cohort, hyperactive was the most common subtype in 91.2% of ICU/IMV patients and in 58.5% of non-ICU patients. Similar to data reported in pre-COVID-19 studies,¹⁰ in this report, patients with hypoactive delirium were more likely to die, despite comparable disease severity. Furthermore, they were older and had higher rates of hypertension. However, they had lower rates of in-hospital complications. A possible explanation for these differences is that in our cohort, hyperactive delirium was most commonly diagnosed in patients who underwent IMV. This finding could be biased because of the unprecedented and sustained high rates

of patients requiring IMV and the shortage of ICU beds during the pandemic.³⁹ Furthermore, because CAM-based tools are less sensitive to detect hypoactive delirium, the latter may be underreported.⁴⁰

To this date, none of the published studies detailing the characteristics of patients with COVID-19 and in-hospital delirium include a description of other COVID-19-associated neurologic symptoms such as anosmia and dysgeusia,^{11–14,24–26} essential phenomena related to some of the hypotheses on how SARS-CoV-2 might invade the central nervous system.^{18–20} Our analysis did not find an association between the presenting COVID-19-associated neurologic symptoms and the development of in-hospital delirium, even after adjusting for relevant covariables.

Although patients with delirium had elevated inflammatory biomarkers, increased disease severity measured by chest CT, and higher mortality scores, only an NLR \geq 9, a surrogate systemic inflammatory response biomarker widely studied in COVID-19, was associated with in-hospital delirium.⁴¹ Therefore, we hypothesize that the proinflammatory and hypercoagulable state triggered by SARS-CoV-2 (known to cause endothelial activation and dysfunction) may have diminished the strict cerebral blood flow

FIGURE 2. Cox Proportional-Hazards Models for In-Hospital Delirium, According to the Invasive Mechanical Ventilation Requirement.



autoregulation in these patients, promoting blood-brain barrier disruption and making them more susceptible to delirium.^{42,43}

Therapeutic strategies during the pandemic have had several variations. All our studied cases were admitted and treated before the publication of the preliminary report by The RECOVERY Collaborative Group on the use of corticosteroids, which has proven to reduce the mortality rates, requirements of IMV, LOS, and increasing the number of ventilator-free days,^{44,45} some of the factors independently associated with the development of in-hospital delirium in the present report. The question of corticosteroid treatment in patients with COVID-19 and its effect on delirium or long-term outcomes remains unanswered.

This study has several limitations we would like to acknowledge. Although assessing for in-hospital delirium using CAM-based tools is standard of care in our institution, due to our retrospective design, where we collected data from electronic medical records, and due to the time gap between screening to expert evaluation (≤ 24 h), delirium may be underreported. Similarly, we could not accurately determine its severity or duration to describe the in-hospital course. The latter is quite relevant because there is evidence of longer delirium duration in patients with COVID-19 than in the pre-COVID-19 era.¹⁴ Second, as seen in other series, our

delirium rates had significant variation between hospital settings. However, we decided to include ICU and non-ICU patients to study the whole in-hospital spectrum of the disease to explore if some COVID-19-associated neurologic symptoms could be associated with in-hospital delirium development.^{19,46}

Third, other well-known delirium precipitating factors (e.g., timing and doses of sedatives or opioids) were not available for the analysis, which may explain why the use of benzodiazepines was not a risk factor in this study as they were recorded as ever used. In addition, we did not collect data on in-hospital treatments, neuroimaging studies, or other diagnostic tests to rule out other delirium causes. Finally, we were unable to record elements of the Assessment/treatment of pain; Both spontaneous awakening and breathing trials; Choice of analgesia and sedation; Delirium assessment, prevention, and management; Early mobility; Family presence (ABCDEF) bundle, which are recommended strategies to reduce the incidence of delirium and improve ICU patients' care⁸ because these strategies are not standardized in our center; therefore, our results should be interpreted according to each center protocols. In critically ill patients with COVID-19, family visitation (bundle element F) significantly lowered the risk of delirium.¹⁴ However, a meta-analysis of non-COVID-19 patients evaluating the impact of bundle interventions in the ICU found that these strategies had no effect on its prevalence and duration or in-hospital mortality, but they were effective in reducing the LOS.⁴⁷

CONCLUSION

In this cohort of patients with confirmed COVID-19 pneumonia, the incidence of in-hospital delirium was 16.3%. Age, IMV, and $\text{NLR} \geq 9$ at hospital admission were independent risk factors for delirium development. Notably, SARS-CoV-2-related neurologic symptoms were not associated with in-hospital delirium. Given the extensive number of active COVID-19 cases worldwide, it is essential to detect patients who are most likely to develop delirium during hospitalization. Improving its preventive measures may reduce the risk of the long-term cognitive and functional sequelae associated with this neuropsychiatric complication.

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure: The authors disclosed no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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