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Incidence, Predictors and Outcomes of Delirium in Critically Ill Patients With COVID-19

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Abstract

Background and Purpose: A variety of neurological manifestations have been attributed to COVID-19, but there is currently limited evidence regarding risk factors and outcomes for delirium in critically ill patients with COVID-19. The purpose of this study was to identify delirium in a large cohort of ICU patients with COVID-19, and to identify associated features and clinical outcomes at the time of hospital discharge. **Methods:** This is an observational cohort study of 213 consecutive patients admitted to an ICU for COVID-19 respiratory illness. Delirium was diagnosed by trained abstractors using the CHART-DEL instrument. The associations between key clinical features, sedation and delirium were examined, as were the impacts of delirium on clinical outcomes. **Results:** Delirium was identified in 57.3% of subjects. Delirious patients were more likely to receive mechanical ventilation, had lower P: F ratios, higher rates of renal replacement therapy and ECMO, and were more likely to receive enteral benzodiazepines. Only mechanical ventilation remained a significant predictor of delirium in a logistic regression model. Mortality was not significantly different, but delirious patients experienced greater mechanical ventilation duration, ICU/hospital lengths of stay, worse functional outcomes at discharge, and were less likely to be discharged home. **Conclusions:** Delirium is common in critically ill patients with COVID-19 and appears to be associated with greater disease severity. When present, delirium is associated with worse functional status at discharge, but not increased mortality. Additional studies are necessary to determine the generalizability of these results and the impact of delirium on longer-term cognitive and functional outcomes.

Keywords

COVID-19, SARS-CoV-2, delirium, acute encephalopathy, ARDS

Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in a global pandemic, with a significant and increasing disease burden in the United States.[1] Illness due to SARS-CoV-2, known as coronavirus disease 2019 (COVID-19), most commonly causes respiratory symptoms of varying severity, but numerous reports have also documented neurological manifestations including altered mental status, stroke and encephalitis.[2-7] Since other coronaviruses have known neurotropism and the angiotensin-converting enzyme 2 (ACE2) receptor used by SARS-CoV-2 to invade host cells is expressed in neurons and glial cells of the CNS, there is potential for direct CNS invasion by the virus.[8-10]

Respiratory illness due to COVID-19 frequently requires ICU admission, most commonly due to development of the acute respiratory distress syndrome (ARDS).[11] Critical illness is itself associated with a high burden of neurological illness, most commonly delirium.[12,13] Delirium is a heterogenous condition primarily characterized by fluctuating inattention and cognitive impairments.[14] The pathogenesis of delirium in ICU patients is complex, with side effects of sedative and analgesic medications, poor sleep hygiene and systemic effects of the underlying disease itself all contributing.[14,15] Multiple studies have confirmed a high incidence of delirium

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in critical illness, particularly ARDS, and there is a consistent association between ICU delirium and long-term cognitive impairments.[16-18]

ICU patients with COVID-19 are frequently isolated, require prolonged mechanical ventilation, are immobilized and may receive higher levels of sedation to reduce the likelihood of circuit disconnection and self-extubation, which are associated with virus aerosolization and increased risk of healthcare worker and nosocomial transmission. These factors, combined with the possibility of direct viral effects on the CNS, have led to speculation that COVID-19 critical illness may be associated with a particularly high burden of delirium.[19,20] However, there are currently very few published studies investigating delirium incidence and associated features, and to our knowledge the impact of delirium on discharge disposition and functional outcomes in critically ill patients has not been described. The majority of studies examining delirium in COVID-19 are small case reports or series, while larger studies frequently do not use validated delirium assessment instruments or are drawn from patients outside of an ICU setting.[21-28] Consequently, the goal of this study is to characterize the incidence of delirium in a large, consecutive observational cohort of patients with COVID-19-associated critical illness, and to describe its associated features and outcomes.

Methods

Overview

This is a single-center cohort study designed to determine the incidence and clinical correlates of delirium in adult patients admitted to an intensive care unit (ICU) with respiratory disease due to COVID-19. The study was reviewed by the institutional review board (IRB) at the University of Michigan and granted a waiver of informed consent, and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Patients

Subjects included all patients age 18 and up with respiratory illness and laboratory-confirmed SARS-CoV-2 infection admitted to an ICU at a single academic medical center from March 9, 2020 to July 5, 2020. Eligible patients were identified both prospectively by active surveillance of all intensive care units, including temporary ICUs, and retrospectively by querying the hospital administrative database. Respiratory illness was defined broadly as the presence of abnormal infiltrates on chest imaging or the need for supplemental oxygen. Excluded patients included those admitted to an ICU without respiratory disease, typically for postoperative monitoring. Eligible patients discharged from an ICU prior to study initiation on May 4, 2020 were identified by querying our institution's COVID-19 administrative dataset for patients who had been admitted to an ICU for any portion of their hospital stay. The COVID-19 dataset includes all patients who have tested positive for SARS-CoV-2 at our institution, or who carried a diagnosis of COVID-19, as determined by ICD-10 codes U07.1 or U07.2, at any point.

Data Collection

Using standard forms and definitions, the complete electronic medical records for all patients were reviewed by trained abstractors. All data were entered into a Research Electronic Data Capture (REDCap) database hosted by the University of Michigan.[29] Data abstractors were a board-certified neurologist and neurointensivist (CAW), a board-certified neurologist and neurocritical care fellow (LO) and 2 senior neurology residents (AN and LF). In addition to neurological training, all abstractors had experience providing direct ICU care to patients with COVID-19. Delirium is typically screened for in ICUs at our institution using the CAM-ICU scale.[30] However, to accommodate the surge of patients with COVID-19 requiring critical care, many patients were cared for in a newly established COVID ICU or other specialty ICUs where protocolized delirium screening is not routinely performed. In addition, many non-ICU nurses without experience using CAM-ICU were shifted to critical care units, resulting in variable performance and documentation of delirium screening. Consequently, the primary outcome of delirium was identified by medical record review using the CHART-DEL instrument, which has previously been validated and found to have 74% sensitivity, 83% specificity and accuracy of 82%.[31] In some cases, medical record review was supplemented by the abstractor's direct experience caring for patients on the Adult COVID Critical Care service or Neurocritical Care Consult service. All instances of delirium identified by abstractors were confirmed via medical record review by the primary author (CAW).

In addition to the presence of delirium, demographic, past medical history and clinical information was obtained by review of the electronic medical record. Disease severity was assessed by the ratio of partial pressure of oxygen to fraction of inspired oxygen (P: F) at the time of ICU admission and at its lowest point. When arterial blood gas data was unavailable, the ratio of hemoglobin saturation to fraction of inspired oxygen (S: F) was obtained, and converted to P: F values using the formula described by Pandharipande et al.[32] Disease severity was further assessed by the need for renal replacement therapy, extracorporeal membrane oxygenation (ECMO), and inflammatory markers at hospital admission (CRP and ferritin). For patients requiring mechanical ventilation, the use of sedative and analgesic medications was recorded. Because dexmedetomidine, enteral benzodiazepines and enteral opioids were frequently started after the appearance of delirium, only patients initiated on these medications prior to delirium onset were compared. Functional outcome at discharge was assessed using both discharge disposition and the modified Rankin scale (MRS), with an MRS value less than

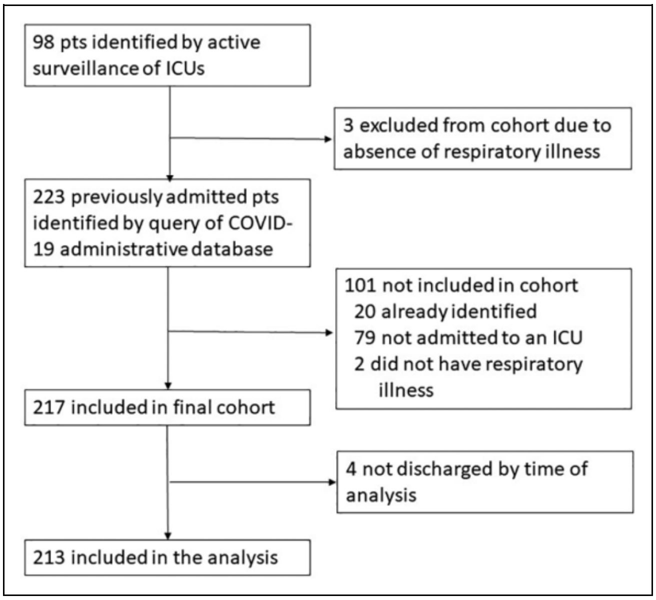

Figure 1. Flowsheet of patients considered for and included in the final analysis cohort.

3 corresponding to functional independence with activities of daily living.[33] MRS values were primarily obtained by review of physical and occupational therapy notes.

Data Analysis

Characteristics of the patient cohort were summarized by determining the median and interquartile range for continuous variables and number and percentage for categorical variables. These characteristics were compared between patients with and without delirium using a 2-sample t-test or the Wilcoxon rank sum test for continuous variables, and the Chi-squared or Fisher Exact test for categorical variables, as appropriate. After excluding variables with obvious collinearity, all clinical factors that were significantly associated with delirium were then included as predictor variables in a logistic regression model with delirium as the outcome variable. For all analyses, a 2-sided alpha of 0.05 was considered statistically significant. All analyses were performed using SAS, version 9.4.

Results

Patient enrollment information is summarized in Figure 1. A total of 98 patients with SARS-CoV-2 infection were identified by active surveillance of all ICUs. Of these, 2 patients admitted to an ICU for postoperative monitoring were excluded because they did not develop respiratory symptoms during their ICU stay, and 1 patient admitted with intracranial hemorrhage was excluded because he developed severe delirium prior to developing COVID-19-associated respiratory illness. Query of the electronic database of COVID-19 cases identified an additional 223 potentially eligible patients, of whom 101 were excluded, most commonly because they were previously identified or were never actually admitted to an ICU. An additional 2 patients who lacked respiratory symptoms were also excluded, yielding a final cohort of 217 patients. Of these, 4 patients had not been discharged at the time of final analysis and were excluded, leaving 213 patients included in the analysis.

Table 1. Demographic and Clinical Characteristics of the Study Population.

Feature	Median (IQR) or N (%)
Age	59.0 (49.0-70.0)
Male gender	131 (61.5)
Race	
African-American	89 (41.7)
White	100 (46.9)
Asian	4 (1.9)
Other/not reported	20 (9.4)
BMI	32.4 (26.0-37.8)
Past medical history	
Diabetes	94 (44.1)
Hypertension	136 (63.9)
Pulmonary disease	59 (27.7)
CAD	40 (18.8)
Neurological disease	50 (23.5)
Cerebrovascular disease	25 (11.7)
Immunosuppression	29 (13.6)
P:F at ICU admission	129.0 (88.0-210.7)
Lowest P:F	86.5 (64.0-127.2)
Mechanical ventilation	160 (75.1)
Mechanical ventilation duration	19.0 (10.0-32.0)
Renal replacement therapy	63 (29.6)
ECMO	19 (8.9)
Admission CRP	13.8 (6.8-24.5)
Admission ferritin	1089.9 (470.9-1573.0)
ICU LOS	16.0 (8.0-29.0 0
Hospital LOS	23.0 (13.0-42.0)
Mortality	63 (29.6)
Discharged home	76 (35.7)
Functionally independent at discharge*	54 (25.4)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; P:F, partial pressure of oxygen: fraction of inspired oxygen; ECMO, extracorporeal membrane oxygenation; CRP, C-reactive protein; LOS, length of stay.

* Modified Rankin Scale < 3.

Overall characteristics of the analysis cohort are summarized in Table 1. The median age was 59, while 62 percent of the population was male. Approximately 47 percent was white, while 42 percent were African-American. Common comorbidities included diabetes in 44 percent, hypertension in 64 percent, pulmonary disease in 28 percent, history of neurological disease in 24 percent and immunosuppression in 14 percent. Seventy-five percent of patients received mechanical ventilation for a median duration of 19 days. Nearly 30 percent of patients died during their hospitalization, while approximately 36 percent were discharged home.

Delirium was detected in 122 (57.3%) patients. Hyperactive delirium only was present in 34%, hypoactive-only

Table 2. Comparison of Delirious and Non-Delirious Patients.

	Delirium (n = 122)	No delirium (n = 91)	p
Age	59.0 (44.0-70.0)	48.0 (51.0-70.0)	0.65
Male gender	77 (63.1)	54 (59.3)	0.52
PMH neuro disease	31 (25.4)	19 (20.9)	0.47
PMH cerebrovascular	16 (13.1)	9 (9.9)	0.47
Mechanical ventilation	107 (87.7)	53 (58.2)	<0.0001
Initial P:F ratio	120.0 (82.0-181.0)	147.0 (107.0-253.0)	0.006
Worse P:F ratio	75.5 (59.0-117.5)	105.0 (67.0-156.0)	0.004
CRP	16.0 (7.4-28.2)	10.2 (6.5-19.9)	0.01
Ferritin	1116.5 (466.0-1670.0)	926.3 (486.2-1390.0)	0.34
Renal replacement therapy	44 (36.1)	19 (20.9)	0.01
ECMO	16 (13.1)	3 (3.3)	0.01
Propofol infusion	104 (97.2)	49 (92.5)	0.17
Opioid infusion	104 (97.2)	51 (96.2)	0.33
Midazolam infusion	72 (67.2)	29 (54.7)	0.12
Cisatracurium infusion	64 (59.8)	29 (54.8)	0.62
Dexmedetomidine infusion	44* (41.1)	27 (50.1)	0.33
Enteral opioids	49* (45.8)	17 (32.1)	0.10
Enteral benzodiazepines	35* (32.7)	9 (17.0)	0.04

Abbreviations: PMH, past medical history; P:F, partial pressure of oxygen: fraction of inspired oxygen; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

The denominator for percentages of sedative agents is the number who received mechanical ventilation (107 delirious and 53 non-delirious patients).

* Because of the large number of patients who received these agents either for treatment or later in hospital course after delirium was present, this number excludes patients who only received these agents after delirium was diagnosed.

delirium in 10%, and both hypoactive and hyperactive in 56%. A comparison of demographic and clinical characteristics of patients with and without delirium is shown in Table 2. Delirious patients were much more likely to receive mechanical ventilation (88% vs. 58%, $p < 0.0001$). Delirious patients also had lower P: F ratios (75.5 vs. 105.0, $p = 0.004$) and were more likely to receive renal replacement therapy (36% vs. 21%, $p = 0.01$) and ECMO (13% vs. 3%, $p = 0.01$).

Sedation management is also detailed in Table 2. The overwhelming majority of ventilated patients received propofol and opioid infusions, without significant differences between groups. Fentanyl was used in 98% of patients receiving opioid infusions. Midazolam was used in all patients receiving benzodiazepine infusions, and its use was more frequent in patients with delirium (67% vs. 55%), but this difference was not statistically significant ($p = 0.12$). Cisatracurium was the only paralytic infusion given at our institution, and its usage did not significantly differ between the 2 groups. Likewise, dexmedetomidine infusion and enteral opioid use did not differ between groups. Delirious patients were, however, significantly more likely to receive enteral benzodiazepines for sedation (33% vs. 17%, $p = 0.04$).

Table 3 details clinical outcomes for patients with and without delirium. Mortality did not significantly differ between delirious and non-delirious patients, but delirious patients were less likely to be discharged home (29% vs. 45%, $p = 0.01$), and much less likely to be functionally independent at discharge (13% vs. 42%, $p < 0.0001$). They also experienced greater durations of mechanical ventilation and longer lengths of stay.

Table 3. Outcomes of Delirious and Non-Delirious Patients.

	Delirium (n = 122)	No delirium (n = 91)	p
ICU LOS	23.0 (14.0-33.0)	9.0 (4.0-16.0)	<0.0001
Hospital LOS	34.5 (21.0-50.0)	13.0 (8.0-21.0)	<0.0001
Mechanical ventilation days	23.0 (13.0-36.0)	11.0 (7.0-19.0)	<0.0001
Mortality	31 (25.4)	31 (34.1)	0.17
Discharged home	35 (28.7)	41 (45.1)	0.01
MRS < 3 at discharge	16 (13.1)	38 (41.8)	<0.0001

Abbreviations: LOS, length of stay; MRS, modified Rankin scale.

In addition to age and gender, all statistically significant features in Table 2 were included in a logistic regression model with delirium as the outcome variable, except for the P: F ratio at ICU admission which was excluded due to clear collinearity with the worse P: F ratio. Odds ratios and 95% confidence intervals for each covariate in the logistic regression model are shown in Table 4. After adjusting for other features, receipt of mechanical ventilation was the only statistically significant predictor of delirium.

Discussion

Results from this study demonstrate that the majority of patients with COVID-19-associated respiratory disease requiring ICU care at a single academic medical center developed delirium during their hospital stay. Delirium was

Table 4. Logistic Regression Model of Delirium Occurrence.

	Odds ratio	95% CI	p
Age	1.01	0.99-1.03	0.40
Male sex	1.00	0.53-1.91	0.99
Mechanical ventilation	3.31	1.50-7.29	0.003
Worse P:F	1.00	0.99-1.00	0.34
CRP	1.02	0.99-1.05	0.15
Renal replacement therapy	1.10	0.53-2.26	0.81
ECMO	2.78	0.55-14.03	0.22
Enteral benzodiazepines	1.90	0.76-4.76	0.17

Abbreviations: CI, confidence interval, P:F, ratio of partial pressure of oxygen to fraction of inhaled oxygen; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation.

associated with greater disease severity, as indicated by the need for mechanical ventilation, P: F ratio, baseline CRP, and receipt of renal replacement therapy and ECMO. When present, delirium was not associated with increased mortality, but delirious patients had significantly longer ICU and hospital length of stays and were substantially less likely to be discharged home and to be functionally independent at the time of discharge. After adjustment for demographic and disease severity covariates, only the receipt of mechanical ventilation remained significantly associated with delirium.

There are few cohorts of critically ill patients with COVID-19 available for comparison, but the frequency of delirium identified in this study is similar, though somewhat lower, than prominent historical cohorts of patients with severe critical illness or ARDS. In the BRAIN-ICU study, 74% of critically ill patients with respiratory failure or shock developed delirium, and longer duration of delirium was independently associated with worse long-term cognitive outcomes.[16] In a nested cohort study within the Awakening and Breathing Controlled (ABC) randomized trial, delirium was identified in 84% of subjects and was similarly associated with worse long-term cognitive outcomes.[34] However, more recent trials in identical populations have suggested that the incidence has decreased to less than 50%.[35]

The incidence of delirium described in the current study is very similar to the large, multicenter cohort described by Pun et al, who noted a 54.9% delirium incidence.[36] As in the current study, mechanical ventilation and benzodiazepine use were associated with delirium in this cohort. However, in contrast to our study, Pun et al do not describe the impact of delirium on patient outcomes, and a large number of patients housed in temporary ICUs were not included in the study, potentially affecting results.

To our knowledge, the only other comparable cohort of ICU patients was recently described by Khan et al, who noted that delirium occurred in 215 of 268 (80.2%) ICU patients admitted to two Midwestern United States academic hospitals.[37] As with our study, delirium was associated with receipt of mechanical ventilation, lower P: F ratio and other markers of disease severity. They similarly found that delirium was significantly associated with greater ICU and hospital length of stay but not mortality. Discharge disposition and functional outcome data was also not reported in this study. In another cohort of 150 critically ill patients admitted to 2 ICUs at a single tertiary referral center in France, delirium was prospectively identified in 97 (64.7%) patients.[38] This study combined patients with either delirium or an abnormal neurological examination in their reported results, so it is not possible to compare outcomes and associated features in this cohort.

There is some evidence that the incidence of ICU delirium is decreasing in recent years, as more centers adopt protocolized delirium monitoring and evidence-based interventions, such as limiting the use of benzodiazepines.[39] However, the COVID-19 pandemic has strained ICU resources across the United States, and legitimate concerns that COVID-19 may be associated with a particularly high frequency of delirium have been raised. In this regard, it is reassuring that the frequency of delirium in this study is lower than prominent historical cohorts. At our institution, a COVID-19-specific protocol for sedation, analgesia, paralysis and delirium was adapted from the 2018 Society of Critical Care Medicine clinical practice guideline for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS),[17] and implemented in all ICUs providing care to patients with COVID-19. It is certainly possible that protocolized care contributed to a lower incidence of delirium compared with historical ARDS cohorts. However, it should be noted that the validated CHART-DEL instrument used in this study is known to be more specific than sensitive, and of course has not been validated in the context of a pandemic surge that could potentially affect the accuracy and completeness of charting.

This study does not allow the differentiation of typical cases of ICU delirium from any in which neuroinvasive SARS-CoV-2 may have played a causative role. However, available data suggest that encephalitis is an infrequent complication of SARS-CoV-2, while delirium is quite common in both ARDS and critical illness in general, and the few available studies do not suggest a substantially higher incidence of delirium in COVID-19.[5,23,37,38] Greater COVID-19 disease severity does appear to be associated with higher incidence of delirium, with the need for mechanical ventilation emerging as the only statistically significant predictor in multivariable logistic regression analysis. Scheduled enteral benzodiazepines, typically lorazepam, were commonly used for sedation of mechanically ventilated patients in our cohort, and in univariate analysis this was the only sedation practice significantly associated with delirium, though the study was not designed specifically to detect an association with sedation practices. It is possible that higher doses or durations of other agents are also associated with delirium. Though delirium incidence was strongly associated with greater ICU and hospital length of stay and worst functional status at discharge, it is not possible to determine whether delirium is causative, or whether these findings are due to greater disease severity or other confounding factors.

Major study limitations include the reliance on accurate charting of delirium symptoms or diagnosis to facilitate retrospective identification. Additionally, the study cohort was obtained at a single academic referral center, so the findings may not generalize to other institutions. Strengths of the study include the use of a validated delirium detection instrument by neurologists experienced in both diagnosing and treating delirium as well as providing critical care to patients with COVID-19. Additional strengths include a relatively large and diverse sample of COVID-19 patients who were cared for in a variety of ICU settings. To our knowledge, this is the first study to both comprehensively assess delirium and its associated features in a cohort of critically ill patients with COVID-19, and to evaluate the impact of delirium on mortality and functional outcome at discharge. Follow-up study of this and other cohorts will be vital in order to determine the impact of delirium on long-term cognitive and functional status in survivors of COVID-19 critical illness.

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Declaration of Conflicting Interests

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