Original Research Article

Demographic Features, Physical Examination Findings, and Medication Use in Hospitalized, Delirious Patients With and Without COVID-19 Infection: A Retrospective Study

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Background: *Delirium is common in the setting of infection with severe acute respiratory syndrome coronavirus 2. Anecdotal evidence and case reports suggest that patients with delirium in the setting of Coronavirus 2019 (COVID-19) may exhibit specific features, including increased tone, abulia, and alogia.* **Objective:** *To determine whether differences exist in sociodemographic and medical characteristics, physical examination findings, and medication use in delirious patients with and without COVID-19 infection referred for psychiatric consultation.* **Methods:** *We undertook an exploratory, retrospective chart review of 486 patients seen by the psychiatry consultation service at a tertiary care hospital from March 10 to May 15, 2020. Delirious patients were diagnosed via clinical examination by a psychiatric consultant, and these patients were stratified by COVID-19 infection status. The strata were described and compared using bivariate analyses across sociodemographic, historical, objective, and treatment-related variables.* **Results:** *A total of 109 patients were diagnosed with delirium during the study period. Thirty-six were COVID-19+. Median age was 63 years and did not differ between groups. COVID-19+ patients with delirium were*

more likely to present from nursing facilities (39% vs 11%; Fisher's exact test; P = 0.001) and have a history of schizophrenia (11% vs 0%; Fisher's exact test; P = 0.011). Myoclonus (28% vs 4%; P = 0.002), hypertonia (36% vs 10%; P = 0.003), withdrawal (36% vs 15%; P = 0.011), akinesia (19% vs 6%; P = 0.034), abulia (19% vs 3%; P = 0.004), and alogia (25% vs 8%; P = 0.012) were more common in COVID-19+ patients. COVID-19+ delirious patients were significantly more likely to have received ketamine (28% vs 7%; P = 0.006), alpha-adrenergic agents besides dexmedetomidine (36% vs 14%; P = 0.014), and enteral antipsychotics (92% vs 66%; P = 0.007) at some point. **Conclusions:** *Patients with COVID-19 delirium referred for psychiatric consultation are more likely to reside in nursing facilities and have a history of schizophrenia than delirious patients without COVID-19. Patients with delirium in the setting of COVID-19 may exhibit features consistent with akinetic mutism. Psychiatrists must assess for such features, as they may influence management choices and the risk of side effects with agents commonly used in the setting of delirium.*
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Key words: delirium, COVID-19, SARS-CoV-2, akinetic mutism.

INTRODUCTION

Delirium is a common complication of infection with severe acute respiratory syndrome coronavirus 2, occurring in up to 34% of elderly patients hospitalized for infections with Coronavirus 2019 (COVID-19) and up to 83% of COVID-19+ patients in the intensive care

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unit (ICU) setting.[1–3] In the first wave of the pandemic, altered mental status, for which delirium represents the most common diagnosis, was the sixth most common presenting sign, and the World Health Organization considers delirium to be a key feature of the illness.[4] COVID-19+ patients may be at increased risk of delirium due to several factors including, but not limited to, potential for direct central nervous system invasion by the virus, induction of central nervous system inflammatory mediators, secondary effects of cerebral hypoxia and metabolic dysregulation, and iatrogenic factors.[5–7] Other risk factors for delirium in the setting of COVID-19 appear to be similar to those for delirium more broadly, including advanced age, severe illness, and medication burden.[3,8] In the ICU setting, mechanical ventilation; use of restraints; benzodiazepine, opioid, and vasopressor infusions; and antipsychotics were each associated with a higher risk of delirium.[8] Notably, social isolation has also been proposed as an additional risk factor for delirium in COVID-19+ patients.[5]

COVID-19+ patients with delirium have a mortality rate of up to 25%, compared to 16% in patients without delirium.[8] Furthermore, delirium in ICU patients with COVID-19 was found to be predictive of worse verbal memory performance at 6 months after discharge in 1 study, and it may be a risk factor for long-term memory impairment in these patients.[8,9]

Prior studies have provided mixed results regarding motoric subtypes of delirium in COVID-19+ patients. Khan et al.[3] suggested that up to 87% of COVID-19+ patients with delirium in the ICU exhibit predominantly hypoactive features. Conversely, Helms et al.[10] reported hyperactive subtype in 86% of COVID-19+ patients diagnosed with delirium, noting an unusual state of agitation when neuromuscular blockers were stopped. Patients with hypoactive delirium in the setting of COVID-19 have been noted to have higher mortality, higher frequency of pulmonary infections, higher frequency and duration of invasive mechanical ventilation, higher frequency of vasopressor support, and longer lengths of hospital stays in a third study.[11] Early reports, including from our own service, highlighted unusual features in many patients with delirium in the setting of COVID-19 including increased muscular tone, immobility, withdrawal (meaning a refusal to eat, drink and/or make eye contact), abulia, and alogia.[12] Such features could be consistent with akinetic mutism (AM), wherein patients are awake but mute and lack spontaneous movement as a result of a profound motivational deficit.[13] AM is a syndrome that can occur in the setting of a variety of illnesses impacting the brain, including delirium. Subsequent studies documented features of AM in up to 13% of COVID-19+ patients, and a study utilizing magnetic resonance spectroscopy in COVID-19+ patients found evidence of delayed posthypoxic leukoencephalopathy, in which AM is a common presentation.[13–15]

Delirium management itself is complex, with multitier considerations of etiology explorations and nonpharmacological and pharmacological strategies.[16] The management of delirium in the setting of COVID-19 is additionally challenging. Many environmental interventions, including frequent reorientation and the use of family supports, are limited by fewer points of contact due to exposure risk and restrictive visitor policies. Reduced time with patients due to infection risk and increased health care demands on staff may impede the identification of emerging delirium. Medications, which are commonly used in the setting of delirium to manage behavioral sequelae and perceptual disturbances, must be chosen carefully to maximize impact while minimizing side effects such as extrapyramidal symptoms and QTc prolongation. These effects may be more common in COVID-19+ patients due to the unique feature of the illness and due to other medications often administered in its treatment.[17–19] Two similar medication algorithms have been proposed and recommended for use in COVID-19+ patients with delirium, each relying on a combination of agents across several different classes.[17,20] Luz et al.[21] found that haloperidol or second-generation antipsychotics remained the main medications selected for delirium management in COVID-19+ patients.

Prior studies have characterized rates, duration, and outcomes of COVID-19 delirium and attempted to identify risk factors for its development. We are not aware of any studies that have examined specific physical features of delirium. Accordingly, we set out to describe sociodemographic and medical characteristics, physical examination findings, and medication use in COVID-19+ patients with delirium seen by our psychiatry consultation service during the pandemic's first wave and compare these features to those of delirious patients without COVID-19 seen during the same timeframe.

METHODS

Study Participants and Procedures

We undertook an exploratory retrospective chart review of electronic health record data from all individuals on both medical and surgical services for whom adult inpatient psychiatric consultation was requested ($n = 486$) at 1 tertiary care hospital in Boston, Massachusetts, United States of America (Massachusetts General Hospital) between March 10, 2020, and May 15, 2020, corresponding to the first wave of the pandemic. For these individuals, we carried out a detailed chart review and analysis for those ($n = 109$) who were diagnosed with delirium by a psychiatrist and for whom some aspect of consultation (i.e., initial and/or follow-up visit) was carried out in-person (given that our institution employed remote consultations for some patients during the early phases of the pandemic). See Figure 1 for information regarding subject inclusion. The study was approved by the Institutional Review Board at Massachusetts General Hospital (protocol # 2020P001392).

Variables and Data Extraction

The following categories of information were manually extracted from the chart for the included individuals: sociodemographic information (age, sex, race, ethnicity, housing status prior to admission, insurance status), past medical and psychiatric histories (including Charlson Comorbidity Index and admission medications), physical examination findings, and treatment interventions.

The stratification variable was COVID-19 infection status, either "negative" or "positive" (COVID-19+) as defined primarily by laboratory confirmation. For 2 subjects (2%), there was strong clinical suspicion for COVID-19 infection despite an absence of laboratory confirmation, and these were included in this study as COVID-19+; for 14 subjects (13%), there was low clinical concern for COVID-19 infection but no laboratory confirmation, and these were included in this study as COVID-19-negative.

To minimize the effects of recall error, missing data, and other biases, variables were operationally defined by specific parameters and collected by pre-specified systematic protocols.[22,23] Data extraction was carried out by 8 independent reviewers, each of whom followed a step-by-step guide for extraction. Reviewers had the option to flag any data about which there was uncertainty, and these entries were adjudicated by at least 2 of 3 additional authors (A.B., N.B., and/or S.R.B.).

Missing Data

No subjects meeting inclusion criteria had >10% incompleteness for variables of interest. Two-thirds of collected variables were 100% complete. Two variables (ethnicity and presence of frontal release signs) were >20% incomplete and were excluded from bivariate comparisons. Sensitivity analysis was carried out by

FIGURE 1. Flow Diagram for Subjects Included in the Study
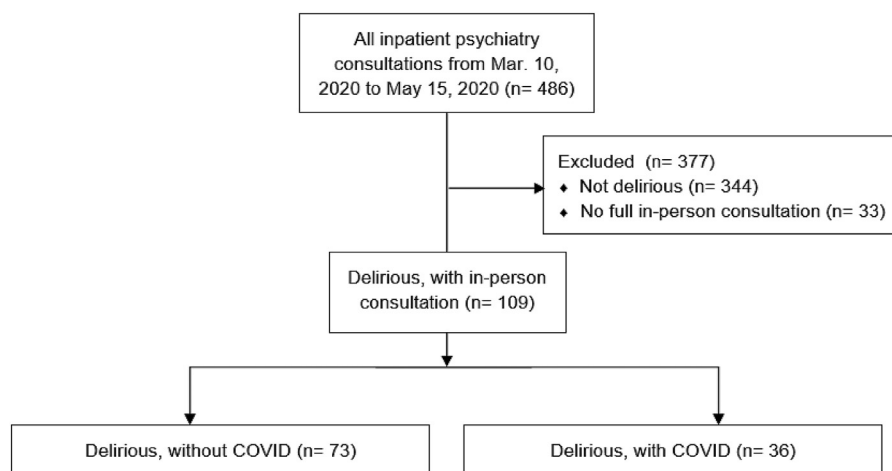
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comparing proportion of missing entries between stratification groups for each variable with ≤20% incompleteness, and these were nonsignificant unless noted.

Statistical Analysis

Univariate statistics were used to examine the variable distributions overall and stratified by COVID-positivity status. Bivariate analyses were conducted to compare COVID-19+ and COVID-19-negative subjects. Student's independent samples *t*-test was used to compare means for the normally distributed continuous variable (i.e., "lowest systolic blood pressure prior to consultation"). Normality was assessed using the Shapiro-Wilk test using an alpha level of 0.05. Mann-Whitney U tests were used to assess median differences for nonnormally distributed continuous variables. Pearson's chi-square tests with Yates' correction were used to examine any difference in expected and observed proportions by COVID status. Where sparse data caused expected counts in contingency tables to be <5, Fisher's exact tests were utilized to obtain P values. Given the descriptive and exploratory nature of this analysis, we did not undertake correction for multiple comparisons, and significance was determined by $P < 0.05$. Data analyses were conducted using jamovi 2.0.0.0 (the jamovi project, https://www.jamovi.org) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA).

RESULTS

Descriptive and Bivariate Analyses

Characteristics of the study sample are presented in Table 1 for COVID-19+ and COVID-19-negative patients separately and for the total sample in aggregate. Also included in these tables are bivariate statistics comparing the COVID-19 infection status groups.

Sociodemographic and Medical Information

Overall, approximately 59% of the sample was male, and sex distribution was not significantly different between infection status groups. The median age was 63 years and did not significantly differ between groups ($P = 0.61$). The total sample was approximately 77% Caucasian, with racial distributions not differing significantly between groups ($P = 0.69$). Ethnicity was not analyzed due to missingness. Housing status prior

to admission was notable for significantly greater proportion of COVID-19+ delirious patients coming from skilled nursing or subacute rehabilitation facilities (39% vs 11%; Fisher's exact test; $P = 0.001$). Insurance status did not differ between groups ($P > 0.99$).

Age-related Charlson Comorbidity Index was not significantly different between groups ($P = 0.062$), with an overall median of 5. Prior-to-admission psychoactive medications did not differ significantly. Overall, approximately 20% had been prescribed benzodiazepines, 22% opioids, 11% medications with anticholinergic effect, and 34% antipsychotics. COVID-19+ patients were more likely to have a history of schizophrenia (11% vs 0%; $P = 0.011$). Other medical and psychiatric variables did not differ between groups.

Features of Clinical Examination

Clinical examination findings are presented in Table 2. Delirium subtype distribution overall was approximately 45% hyperactive, 26% hypoactive, and 29% mixed; these did not significantly differ between groups. All the following were seen significantly more often in the COVID-19+ group: myoclonus (28% vs 4%; $P = 0.002$), hypertonia (36% vs 10%; $P = 0.003$), withdrawal (36% vs 15%; $P = 0.011$), akinesia (19% vs 6%; $P = 0.034$), abulia (19% vs 3%; $P = 0.004$), and alogia (25% vs 8%; $P = 0.012$). Tremor (20% overall), restlessness (41% overall), agitation (68% overall), and paranoia/delusions (20% overall) did not differ between groups. Presence of auditory and/or visual hallucinations also did not differ significantly between groups (26% overall). Frontal release signs were not analyzed due to missingness.

Treatment Interventions

Treatment interventions are presented in Table 3. COVID-19+ delirious patients were significantly more likely to have received the following at some point during their admissions: ketamine (28% vs 7%; $P = 0.006$), alpha-adrenergic agents other than dexmedetomidine (36% vs 14%; $P = 0.014$), and enteral antipsychotics (92% vs 66%; $P = 0.007$). The use of other medications at any point during admission did not differ significantly between groups. Median day of psychiatric consultation was significantly later in the COVID+ group (7 days vs 3 days; $P = 0.042$).

TABLE 1. Baseline, Historical, and Admission Characteristics

Variable	Total	COVID (−)	COVID (+)	Test statistic (df)	Total cohort (N = 109)* P value
Male sex	64 (59)	42 (58)	22 (61)	$\chi^2 = 0.02$ (1)	0.88
Age, y (median)	63	61	68	U = 1235	0.61
Race					0.69[†]
White	84 (77)	60 (82)	24 (67)		
Black	6 (6)	4 (6)	2 (6)		
Asian	2 (2)	1 (1)	1 (3)		
Other	5 (5)	5 (7)	2 (6)		
Housing status					**0.001**[†]
Domiciled	75 (69)	55 (75)	20 (56)		
Undomiciled	10 (9)	9 (12)	1 (3)		
SNF/SAR	22 (20)	8 (11)	14 (39)		
Acute rehab	1 (1)	0 (0)	1 (3)		
Insurance status					>0.99[†]
Insured	104 (95)	69 (95)	35 (97)		
Uninsured	2 (2)	2 (3)	0 (0)		
History of schizophrenia	4 (4)	0 (0)	4 (11)		**0.011**[†]
History of prior delirium	52 (48)	36 (49)	16 (44)	$\chi^2 = 0.18$ (1)	0.67
History of AUD	47 (43)	33 (45)	14 (40)	$\chi^2 = 0.48$ (1)	0.49
History of other NCD	33 (30)	22 (30)	11 (31)	$\chi^2 = 0.00$ (1)	>0.99
CCI age-related (median)	5	5	4	U = 1026	0.062
PTA psychoactive medication					
Benzodiazepines	22 (20)	13 (18)	9 (25)	$\chi^2 = 0.39$ (1)	0.531
Opioids	24 (22)	19 (26)	5 (14)	$\chi^2 = 1.42$ (1)	0.233
Anticholinergics	12 (11)	7 (10)	5 (12)		0.526[†]
Antipsychotics	37 (34)	22 (30)	15 (37)	$\chi^2 = 0.96$ (1)	0.327

Missingness—race: total = 12, Covid (−) = 5, Covid (+) = 7. Housing status: total = 1, Covid (−) = 1, Covid (+) = 0. Insurance: total = 3, Covid (−) = 2, Covid (+) = 1. History of schizophrenia: total = 4, Covid (−) = 3, Covid (+) = 1. History of prior delirium: total = 8, Covid (−) = 6, Covid (+) = 2. History of AUD: total = 10, Covid (−) = 8, Covid (+) = 2. History of NCD: total = 3, Covid (−) = 2, Covid (+) = 1. Data are presented as number (%) unless otherwise indicated.

χ^2 = Pearson's Chi-squared test with Yates' correction; AUD = alcohol use disorder; CCI = Charlson Comorbidity Index; NCD = neurocognitive disorder; PTA = prior to admission; SNF/SAR = skilled nursing facility/subacute rehab; U = Mann-Whitney Wilcoxon Test. Bolded values indicate statistical significance ($P < 0.05$).

* Missing data.
[†] Fisher's exact test.

DISCUSSION

Overall, patients with delirium in the setting of COVID-19 were more likely to reside in nursing facilities and to have a history of schizophrenia than their counterparts with delirium who tested negative for COVID-19. COVID-19+ patients referred for psychiatric consultation also exhibited higher rates of several neurological findings and were more likely to receive certain medications, including ketamine, some alpha-adrenergic agents, and enteral antipsychotics. Demographic findings in our study are consistent with prior studies of COVID-19 delirium. A higher proportion of delirious patients were men, similar to findings in earlier studies.[11] Notably, our COVID-19+ sample, with a median age of 68 years, was slightly older than

other cohorts with median ages of 60 and 54 years.[3,11] We found no racial differences between COVID-19+ delirious patients and delirious patients without COVID, which were both consistent with overall demographics of hospitalized patients at our institution. Unfortunately, we could not analyze differences in ethnicity due to missing data, which may have been relevant given that Latinx patients in our community were disproportionately affected by the pandemic. There were no differences in age-related Charlson Comorbidity Index. COVID-19+ delirious patients seen by our service were significantly more likely to present from skilled nursing or subacute rehabilitation facilities. In the first wave of the pandemic, these congregate settings were frequent sites of COVID-19 outbreaks, which may account for the overrepresentation in our

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TABLE 2. Physical Exam and Laboratory Findings in Total Cohort and by COVID Status*

Variable[†]	Total	COVID (−)	COVID (+)	Test statistic (df)	P value
Myoclonus	13 (12)	3 (4)	10 (28)		**0.002**[‡]
Hypertonia	20 (18)	7 (10)	13 (36)	$\chi^2 = 8.91$ (1)	**0.003**
Withdrawal	24 (22)	11 (15)	13 (36)	$\chi^2 = 6.46$ (1)	**0.011**[‡]
Akinesia	11 (10)	4 (6)	7 (19)		**0.034**[‡]
Abulia	9 (8)	2 (3)	7 (19)		**0.004**[‡]
Alogia	15 (14)	6 (8)	9 (25)		**0.012**[‡]
Tremor	22 (20)	12 (16)	10 (28)	$\chi^2 = 1.41$ (1)	0.24
Restlessness	45 (41)	26 (36)	19 (53)	$\chi^2 = 2.19$ (1)	0.14
Agitation	74 (68)	51 (70)	23 (64)	$\chi^2 = 0.17$ (1)	0.68
Paranoia/Delusions	22 (20)	16 (22)	6 (17)	$\chi^2 = 0.01$ (1)	0.91
Perceptual disturbance	28 (26)	20 (27)	8 (22)	$\chi^2 = 0.00$ (1)	>0.99
Motoric subtype				$\chi^2 = 1.71$ (2)	0.43
Hyperactive	49 (45)	35 (48)	14 (39)		
Hypoactive	28 (26)	16 (22)	12 (33)		
Mixed	32 (29)	22 (30)	10 (28)		

Missingness was small and not significantly different between groups for the data presented with the exception of those noted below. Missingness—Perceptual disturbance: total = 12, Covid (−) = 4, Covid (+) = 8, P = 0.013 (Fisher's exact test).

χ^2 = Pearson's Chi-squared test with Yates' correction.

Bolded values indicate statistical significance ($P < 0.05$).

* Data are presented as number (%) unless otherwise indicated.

[†] Variables selected a priori based on clinical judgment and published literature.

[‡] Fisher's exact test.

sample.[24] There were no differences in rates of other neurocognitive disorders or alcohol use disorder between the 2 groups. Notably, all patients with schizophrenia belonged to the COVID-19+ group. From prior literature, schizophrenia is known to be a significant risk factor for COVID-19 infection and for increased morbidity and mortality in the setting of infection.[25,26]

We did not find any differences in motoric subtype by COVID-19 diagnosis but did find hyperactive delirium to be most common in both samples. This finding differs from some prior literature about both

TABLE 3. Interventions Administered at Any Time in Total Cohort and by COVID Status*

Variable[†]	Total	COVID (−)	COVID (+)	χ^2 (df)	P value
Corticosteroids	30 (28)	18 (25)	12 (33)	0.53 (1)	0.47
Vasopressors	41 (38)	25 (34)	16 (44)	0.68 (1)	0.41
Propofol infusion	36 (33)	22 (30)	14 (39)	0.49 (1)	0.49
Opioids	69 (63)	47 (64)	22 (61)	0.15 (1)	0.90
Benzodiazepines	72 (66)	46 (63)	26 (72)	0.55 (1)	0.46
Ketamine	15 (14)	5 (7)	10 (28)	7.22 (1)	**0.006**[‡]
α-Adrenergic agents					
Dexmedetomidine	33 (30)	21 (29)	12 (33)	0.07 (1)	0.79
Other	23 (21)	10 (14)	13 (36)	5.99 (1)	**0.01**
Antipsychotics					
Enteral	81 (74)	48 (66)	33 (92)	7.18 (1)	**0.007**[‡]
Intravenous	67 (62)	44 (60)	23 (64)	0.02 (1)	0.88
Valproate	19 (17)	11 (15)	8 (22)	0.43 (1)	0.51
Physical restraint	81 (74)	54 (74)	27 (75)	0.00 (1)	>0.99

χ^2 = Pearson's Chi-squared test with Yates' correction.

Bolded values indicate statistical significance ($P < 0.05$).

* Data are presented as number (%) unless otherwise indicated.

[†] Variables selected a priori based on clinical judgment and published literature.

[‡] Fisher's exact test.

COVID-19 and non-COVID-19 deliria. The difference likely represents skewed sampling seen by psychiatry consultation services, which are more likely to be involved for patients who are agitated,[27,28] as compared to studies that examined consecutive delirious patients in a particular setting such as the ICU.[3] It may also indicate underrecognition of hypoactive delirium by primary teams or nurse delirium screening instruments tending to include more hyperactive features in their assessments, which has been commonly described.[29,30] Anecdotally, our service observed that patients with COVID-19+ delirium tended to present either with extreme hyperactivity or extreme hypoactivity, as compared to a broader spectrum typically seen. We also did not detect any differences in rates of hallucinations or delusions between the 2 groups despite the difference with respect to history of schizophrenia.

Notably, we did detect differences in several physical examination findings between COVID-19+ patients with delirium and delirious patients without COVID-19 receiving psychiatric consultation. Specifically, while there were no differences in rates of tremor, COVID-19+ patients were more likely to exhibit myoclonus, hypertonia, withdrawal, akinesia, abulia, and alogia. These findings are consistent with early reports about the atypical nature of COVID-19+ delirium.[10,12] Rabano-Suarez et al. reported a series of 3 patients with generalized myoclonus and diffuse slowing on electroencephalogram despite otherwise mild COVID-19 symptoms (e.g., not requiring intubation), and Anand et al. reported a series of 8 critically ill patients with COVID-19 who developed myoclonus in the setting of intubation.[31,32] Multifocal myoclonus is a common feature in delirium and considered indicative of global brain dysfunction, but it is generally not specific or prognostic.[32–34]

The remaining symptoms observed at higher rates among COVID-19+ patients in our study are all features seen in catatonia and AM, which have now both been described in COVID-19+ patients.[12,13,35–38] Anecdotally, patients on our service with these features did not improve with benzodiazepines and lacked other behavioral features of catatonia, suggesting that AM may be the more fitting syndromic descriptor. AM has been described in COVID-19+ patients with severe respiratory illness, with meningoencephalitis, and with pre-existing neuropsychiatric vulnerabilities.[13] AM typically presents after extubation, which would be consistent with the timeframe in which most COVID-19+ patients were seen by our service.[14] One possible explanation for this overrepresentation of AM signs is that the high degree of inflammation seen in many COVID-19+ patients disrupts dopamine synthesis and function. This could lead to a state of dopamine depletion and create a vulnerability to AM through impairment of mesocorticolimbic dopamine signaling required for motivation and movement.[39,40] The high rates of AM could also represent a subtype of delayed posthypoxic leukoencephalopathy which can clinically present with features of dopamine dysfunction such as parkinsonian tremor and rigidity.[41] The increased tone found more often in COVID+ patients with delirium may indicate a greater sensitivity to antipsychotic agents, which may reflect the same dopamine signaling impairments just mentioned, and has important implications for management.

For the most part, the strategies used to manage behavioral symptoms and signs in COVID-19+ and COVID-19-negative patients were similar. Given the older age seen in our sample, the rates of prehospital benzodiazepines (20%), opioids (22%), and anticholinergic medication (11%) prescriptions in both groups are notable and may have constituted additional predisposing risk factors for delirium. A variety of sedative agents, antipsychotic medications, and mood stabilizers were used in both groups, and both groups experienced similar rates of physical restraint. We detected differences in prescribing practices for certain agents however. Primary teams were more likely to use ketamine as an adjunct sedative agent in COVID-19+ patients. We speculate that this may be due to both the high rates of agitation seen in COVID-19+ patients, who often required management with multiple sedative agents, as well as a shift to novel sedative agents during the first wave of the pandemic, as concerns about medication supplies arose. It is also possible that redeployment staffing of ICUs by hospitalists and senior residents led to unique prescribing practices for COVID-19+ patients in those settings. Notably, ketamine has been associated with an increased risk of developing delirium, which could have been a contributing factor in some cases.[42]

While dexmedetomidine was used at similar rates in both groups, other alpha-adrenergic agents like clonidine were more commonly used in patients with COVID-19. This practice likely reflects increased concerns about antipsychotic use due to possible increased risks of extrapyramidal symptoms and QTc prolongation, concerns which aligned with our service's early observations (and thereby, perhaps, recommendations)

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and subsequent published management algorithms for COVID-19+ delirium.[17,20]

While there were no differences in rates of parenteral antipsychotic use between the 2 groups, COVID-19+ patients were significantly more likely to receive oral antipsychotics than COVID-19-negative patients. These findings are surprising, in part because parenteral agents might be expected to be more commonly used in COVID-19+ patients due to ease of administration and decreased risk of exposing nursing staff to the virus. The higher rates of oral antipsychotic use in COVID+ patients, with over 90% of patients receiving at least 1 dose, do not coincide with any differences in motoric subtypes. These higher rates could reflect more aggressive prescribing practices by primary teams for COVID-19+ patients in the setting of feeling overwhelmed or of increased desire to control to even small amounts of activity (e.g., which could have the potential to be care-interfering and require greater staff presence for redirection than was able to be supplied).

Finally, delirious patients with COVID-19 received a psychiatric consultation significantly later in their course of hospitalization than delirious patients without COVID-19, which may have impacted the medications used by primary teams. Many patients with COVID were intubated early in their course, which may have delayed psychiatric consultation. Furthermore, COVID+ patients were often being cared for by physicians deployed to cover medical services who were less familiar with managing inpatients, which could have led to an additional delay in consultation.

Strengths of our study include the determination of a clinical diagnosis of delirium by in-person psychiatric examination, heterogeneity in patient sample (including patients in and out of the ICU setting), and direct physical/motoric examination. Our study was limited by its retrospective nature and relatively small sample size, which prevented the performance of multivariable analyses. Additionally, due to the exploratory nature of these analyses, we did not adjust for multiple comparisons; therefore, results should be interpreted with caution. Another important limitation of this case-control study is possible sampling bias, as we only studied patients referred for psychiatric consultation. As noted above, the higher frequency of hyperactive delirium suggests that the overall sample was skewed, as would be expected on a psychiatry consultation service, and this skewing may affect other analyses,

suggesting that findings may therefore not generalize to all patients with COVID-19+ delirium. We also utilized a large number (8) of chart reviewers. While we attempted to standardize data extraction by creating a step-by-step guide, by having each reviewer complete practice extractions, and by using multiple adjudicators, it is still possible that some interrater reliability was lost. With regard to physical examination findings, examiners may have been more likely to look for signs of AM in COVID-19+ patients given some early observations about such findings. However, neither group had significant missing data regarding these features. Furthermore, the note template for the psychiatry consultation service incorporated these features relatively early in the pandemic once we observed increased rates, so symptoms were assessed in most consultations.

As this study was conducted during the first wave of the pandemic, additional studies are needed to clarify whether similar trends exist with newer variants, especially Omicron, which has lower rates of anosmia than earlier variants,[43] leading some to speculate that rates of delirium may also be lower.

CONCLUSIONS

This study offers support for earlier findings regarding demographic and clinical features of patients with COVID delirium. It is the first study to characterize specific unique features of delirium in COVID-19+ patients and offers further evidence that psychiatrists should be alert to the possibility of AM in these patients.

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