OBSERVATIONAL STUDY

OPEN

Examination of Early CNS Symptoms and Severe Coronavirus Disease 2019: A Multicenter Observational Case Series

David E. Marra, PhD[1]
Katharina M. Busl, MD, MS[2,3]
Christopher P. Robinson, DO, MS[2,3]
Maria J. Bruzzone, MD[2]
Amber H. Miller, MPH[2]
Zhaoyi Chen, PhD[4]
Yi Guo, PhD[4]
Tianchen Lyu, MS[4]
Jiang Bian, PhD[4]
Glenn E. Smith, PhD, ABPP-CN[1]

OBJECTIVES: To determine if early CNS symptoms are associated with severe coronavirus disease 2019.

DESIGN: A retrospective, observational case series study design.

SETTING: Electronic health records were reviewed for patients from five healthcare systems across the state of Florida, United States.

PATIENTS: A clinical sample ($n = 36,615$) of patients with confirmed diagnosis of coronavirus disease 2019 were included. Twelve percent ($n = 4,417$) of the sample developed severe coronavirus disease 2019, defined as requiring critical care, mechanical ventilation, or diagnosis of acute respiratory distress syndrome, sepsis, or severe inflammatory response syndrome.

INTERVENTIONS: None.

MEASUREMENT AND MAIN RESULTS: We reviewed the electronic health record for diagnosis of early CNS symptoms (encephalopathy, headache, ageusia, anosmia, dizziness, acute cerebrovascular disease) between 14 days before the diagnosis of coronavirus disease 2019 and 8 days after the diagnosis of coronavirus disease 2019, or before the date of severe coronavirus disease 2019 diagnosis, whichever came first. Hierarchal logistic regression models were used to examine the odds of developing severe coronavirus disease 2019 based on diagnosis of early CNS symptoms. Severe coronavirus disease 2019 patients were significantly more likely to have early CNS symptoms (32.8%) compared with nonsevere patients (6.11%; $\chi^2[1] = 3,266.08$, $p < 0.0001$, $\varphi = 0.29$). After adjusting for demographic variables and pertinent comorbidities, early CNS symptoms were significantly associated with severe coronavirus disease 2019 (odds ratio = 3.21). Diagnosis of encephalopathy (odds ratio = 14.38) was associated with greater odds of severe coronavirus disease 2019; whereas diagnosis of anosmia (odds ratio = 0.45), ageusia (odds ratio = 0.46), and headache (odds ratio = 0.63) were associated with reduced odds of severe coronavirus disease 2019.

CONCLUSIONS: Early CNS symptoms, and specifically encephalopathy, are differentially associated with risk of severe coronavirus disease 2019 and may serve as an early marker for differences in clinical disease course. Therapies for early coronavirus disease 2019 are scarce, and further identification of subgroups at risk may help to advance understanding of the severity trajectories and enable focused treatment.

KEY WORDS: central nervous system; coronavirus disease 2019; critical care; encephalopathy

Although coronavirus disease 2019 (COVID-19) is primarily considered a respiratory illness, it's multisystem pathology manifests with dysfunction in other systems, including the CNS. Prevalence of CNS symptomology in COVID-19 varies widely based on COVID severity and study

DOI: 10.1097/CCE.0000000000000456

methodology. Nonetheless, CNS symptoms are commonly found in COVID-19 patients (1–3). A systematic review examining 31 studies consisting of hospitalized patients found that 9–17% of patients reported dizziness, 6–33% reported headaches, 8% of patients experienced impairment in consciousness, and 1.6–2.5% of patients suffered ischemic strokes (3). Anosmia and ageusia are also exceedingly common in patients with COVID-19, with reported rates as high as 85% and 88%, respectively (2). An early study from Wuhan, China, showed that patients with severe COVID-19 were more likely to have comorbid CNS symptoms (i.e., impaired consciousness, acute cerebrovascular disease) relative to patients with less severe respiratory issues (1). Conversely, anosmia and ageusia were found to be associated with a milder disease course (1, 4). More recently, several studies have found that the presence of early CNS symptoms (eCNSsx), notably encephalopathy and stroke, predicts increased mortality and worsened outcomes (5–7) in COVID-19 patients. Herein, we aim to address the presence of eCNSsx in COVID-19 as a potential risk factor for disease severity and progression and provide insight into early recognition and therapeutic time windows in COVID-19 as this has not been examined in a large empirical study.

METHODS

This study was approved by the University of Florida's Institutional Review Board (202001860) including waiver of informed consent. De-identified electronic health record (EHR) data were aggregated from the OneFlorida Clinical Research Consortium (8) that is comprised of five partners the University of Florida Health, Tallahassee Memorial Hospital, Orlando Health, University of Miami Health, and AdventHealth. All partners provided weekly EHR updates for a COVID-19 dataset. All partners used Epic as their EHR management software. The dates of extracted clinical data ranged from January 1, 2020, to October 25, 2020. Extracted variables of interest included diagnosis of COVID-19, COVID-19 severity, presence of eCNSsx, demographic variables (age, sex, race, ethnicity), and history of preexisting comorbidities thought to increase risk of severe disease progression course (9).

The present study is an EHR-based retrospective observational case series. The index date for all windows of observation was defined as the date of confirmed COVID-19 diagnosis. For all patients, diagnosis of eCNSsx was identified in the EHRs starting from 2 weeks prior to the index date (the presumed maximum incubation period for the virus [10]) to 8 days after the index date (median number of days from diagnosis to hospitalization [11]) or the date on which the patient developed severe COVID-19, whichever came first.

All patients underwent reverse-transcriptase polymerase chain reaction (PCR)-based clinical testing. To increase diagnostic precision of the coronavirus disease positive (COVID+) sample, a patient was considered COVID+ if all three of the following criteria were met in the EHR: 1) a recorded positive laboratory test result; 2) an associated *International Classification of Diseases*, 10th Revision diagnosis; and 3) manually "flagged" by their healthcare providers as being COVID+ (e.g., based on outside laboratory tests).

Patients were classified as having severe COVID-19 if they required intensive care treatment (i.e., admission to ICU), required mechanical ventilation, or if medical records indicated a diagnosis of sepsis, acute respiratory distress syndrome, systemic inflammatory response syndrome, or hypoxic respiratory failure (**Supplemental Table 1**, http://links.lww.com/CCX/A683). Medical comorbidities observed to increase the risk of severe COVID-19 were also examined (9). Specifically, we examined asthma, hypoxemia, diabetes, chronic kidney disease (CKD), obesity, tobacco use, immunodeficiency, and chronic obstructive pulmonary disease "prior" to COVID infection (i.e., –14 d or earlier from index date). eCNSsx were derived from studies out of Wuhan, China, and Europe and included anosmia, ageusia, dizziness, headache, ataxia, and encephalopathy (1, 2) (**Table 1**). Encephalopathy specifically, included the diagnostic codes for disorientation, altered mental status, impaired consciousness, toxic encephalopathy, metabolic encephalopathy, and encephalopathy NOS due its incongruent definition. Hierarchal logistic regression was conducted to test the hypothesis that eCNSsx was associated with severe COVID-19, after controlling for demographic variables and pertinent comorbidities. The data from this sample is a clinically derived observational sample across multiple institutions. As such, there is an inherent selection bias toward individuals who are physically located near one of the five regional networks that provided data and patients who can afford clinical care in nonemergent cases. Efforts to reduce the effects

TABLE 1.
Prevalence of Comorbidities and CNS Symptoms

Variable of Interest	COVID+, *n* (%)	Nonsevere COVID, *n* (%)	Severe COVID, *n* (%)	Test Statistic
n (%)	36,615 (100)	32,198 (87.9)	4,417 (12.1)	
Comorbidities	**10,295 (28.1)**	**8,137 (25.3)**	**2,158 (48.9)**	**$\chi^2(1) = 1{,}068.99$, $p < 0.0001$, $\varphi = 0.17$**
Asthma	2,023 (5.5)	1,745 (5.4)	278 (6.3)	$\chi^2(1) = 5.68$, $p = 0.017$, $\varphi = 0.01$
Hypoxemia	298 (0.8)	184 (0.6)	114 (2.6)	$\chi^2(1) = 194.29$, $p < 0.0001$, $\varphi = 0.07$
Diabetes	3,823 (10.4)	2,623 (8.1)	1,200 (27.2)	$\chi^2(1) = 1{,}502.88$, $p < 0.0001$, $\varphi = 0.20$
Hypertension	6,936 (18.9)	5,196 (16.1)	1,740 (39.4)	$\chi^2(1) = 1{,}368.08$, $p < 0.0001$, $\varphi = 0.19$
Chronic kidney disease	1,235 (3.4)	742 (2.3)	493 (11.2)	$\chi^2(1) = 934.88$, $p < 0.0001$, $\varphi = 0.16$
Obesity	3,566 (9.7)	2,871 (8.9)	694 (15.7)	$\chi^2(1) = 204.08$, $p < 0.0001$, $\varphi = 0.07$
Tobacco use	1,509 (4.1)	1,202 (3.7)	307 (7.0)	$\chi^2(1) = 101.75$, $p < 0.0001$, $\varphi = 0.05$
Immunodeficiency	93 (0.3)	77 (0.2)	16 (0.4)	$\chi^2(1) = 2.32$, $p = 0.13$, $\varphi = 0.01$
Chronic obstructive pulmonary disease	746 (2.0)	484 (1.5)	262 (5.9)	$\chi^2(1) = 381.64$, $p < 0.0001$, $\varphi = 0.10$
Early CNS symptoms	**3,233 (8.8)**	**1,968 (6.11)**	**1,448 (32.8)**	**$\chi^2(1) = 3{,}266.08$, $p < 0.0001$, $\varphi = 0.29$**
Anosmia	303 (0.8)	292 (0.9)	11 (0.2)	$\chi^2(1) = 20.44$, $p < 0.0001$, $\varphi = 0.25$
Ageusia	191 (0.5)	183 (0.6)	8 (0.2)	$\chi^2(1) = 11.24$, $p = 0.0008$, $\varphi = 0.24$
Headache	1,599 (4.4)	1,488 (4.6)	111 (2.5)	$\chi^2(1) = 40.00$, $p < 0.0001$, $\varphi = 0.15$
Ataxia	7 (< 0.1)	5 (< 0.1)	2 (< 0.1)	$\chi^2(1) = 1.80$, $p = 0.18$, $\varphi = 0.01$
Encephalopathy	1,133 (3.1)	255 (0.8)	878 (19.9)	$\chi^2(1) = 4{,}718.42$, $p < 0.0001$, $\varphi = 0.36$

COVID = coronavirus disease.
Bolded test statistics represent the omnibus analysis; post hoc analyses are not bolded.

of bias were conducted by controlling for gender, ethnicity, and race in all subsequent analyses.

RESULTS

The clinical sample consisted of n = 36,615 COVID+ patients, with 12.1% (n = 4,417) of the sample diagnosed with severe COVID-19 (**Table 2**). Severe COVID patients were significantly older (t[36,613] = 58.67, $p < 0.001$, $d = 0.97$), had a higher proportion of males (χ^2[1] = 143.36, $p < 0.001$, $\psi = 0.06$), and were more likely to be diagnosed with medical comorbidities (χ^2[1] = 1,068.99, $p < 0.0001$, $\varphi = 0.17$). Relative to White patients, self-identified Black patients (χ^2[1] = 41.39, $p < 0.0001$, $\varphi = 0.04$), and those with race listed as "Other" (χ^2[1] = 26.41, $p < 0.0001$, $\varphi = 0.09$) had a greater likelihood of developing severe COVID-19. There were fewer self-identified Hispanic patients with severe COVID-19, relative to non-Hispanics (χ^2[1] = 8.841, $p = 0.003$, $\varphi = 0.02$).

Nearly half (48.9%) of the severe COVID-19 cohort were diagnosed with at least one comorbidity thought to increase the risk of severe COVID, which was significantly higher than the nonsevere group (25.3%; χ^2[1] = 1,068.99, $p < 0.0001$, $\varphi = 0.17$) (Table 1). Severe COVID-19 patients were significantly more likely to be diagnosed with all defined comorbidities, with the exception of immunodeficiency, relative to the nonsevere group (all p's < 0.05). When entered into a hierarchal logistic regression predicting severe COVID-19 (**Table 3**), the odds of developing severe COVID-19 in patients with a preexisting comorbidity was 38% higher in patients with no comorbidities (odds ratio [OR], 1.38; 95% CI, 1.28–1.49). Although there is a higher prevalence of almost all comorbidities in the severe group, an exploratory post hoc analysis found that only pre-COVID diagnosis of hypoxemia (OR, 1.98; 95% CI, 1.51–2.60), diabetes (OR, 1.71; 95% CI, 1.54–2.60), CKD (OR, 1.32; 95% CI, 1.15–1.51), and obesity (OR, 1.12; 95% CI, 1.00–1.25) were associated

TABLE 2.
Demographic Information of Severe and Nonsevere Coronavirus Disease Positive Patients

Variable of Interest	COVID+	Nonsevere COVID	Severe COVID	Test Statistic
n (%)	36,615 (100)	32,198 (87.9)	4,417 (12.1)	
Mean, age (SD)	43.3 (20.5)	41.0 (19.7)	59.4 (18.4)	**$t(36{,}613) = 58.67$, $p < 0.001$, $d = 0.97$**
Sex, *n* (%)				**$\chi^2(1) = 143.36$, $p < 0.001$, $\varphi = 0.06$**
Female	19,868 (54.3)	17,843 (55.4)	2,025 (45.8)	
Male	16,747 (45.7)	14,355 (44.6)	2,392 (54.2)	
Race[a], *n* (%)				**$\chi^2(4) = 4{,}424.37$, $p < 0.001$, $V = 0.17$**
White	14,623 (39.9)	12,717 (39.5)	1,906 (43.2)	
Asian	550 (1.5)	478 (1.5)	72 (1.6)	$\chi^2(1) = 0.56$, $p = 0.46$, $\varphi = 0.00$
Black	7,335 (20.0)	6,145 (19.1)	1,190 (26.9)	$\chi^2(1) = 41.39$, $p < 0.0001$, $\varphi = 0.04$
Other	10,077 (27.5)	8,987 (27.9)	1,090 (24.7)	$\chi^2(1) = 26.41$, $p < 0.0001$, $\varphi = 0.09$
Unknown	4,030 (11.0)	3,871 (12.0)	159 (3.6)	$\chi^2(1) = 246.09$, $p < 0.0001$, $\varphi = 0.34$
Ethnicity[b], *n* (%)				**$\chi^2(2) = 269.15$, $p < 0.0001$, $V = 0.06$**
Non-Hispanic	19,124 (52.2)	16,506 (51.3)	2,618 (59.3)	
Hispanic	11,578 (31.6)	10,122 (31.4)	1,456 (33.0)	$\chi^2(1) = 8.841$, $p = 0.003$, $\varphi = 0.02$
Unknown	5,913 (16.1)	5,570 (17.3)	343 (7.8)	$\chi^2(1) = 250.26$, $p < 0.0001$, $\varphi = 0.10$

COVID = coronavirus disease.
[a]Post hoc comparisons of race compared the proportion of self-identified minorities relative to Whites.
[b]Post hoc comparisons of ethnicity compared with non-Hispanic ethnicity.
Bolded test statistics represent the omnibus analysis; post hoc analyses are not bolded.

with higher odds of severe COVID-19 when all comorbidities were simultaneously entered into a multivariate logistic regression model (**Table 4**). Odds of severe COVID-19 was further increased based on the number of comorbidities, as the odds of severe COVID-19 was significantly higher in patients with 1–2 comorbidities (OR, 1.22; 95% CI, 1.13–1.33) and 3+ comorbidities (OR, 1.84; 95% CI, 1.65–2.04) compared with patients with no comorbidities.

Overall, the proportion of severe COVID patients who displayed eCNSsx (32.8%) was significantly larger than the nonsevere group of COVID patients (6.11%; $\chi^2[1] = 3{,}266.08$, $p < 0.0001$, $\varphi = 0.29$). Severe COVID+ patients were more likely to be diagnosed with encephalopathy ($\chi^2[1] = 4{,}718.42$, $p < 0.0001$, $\varphi = 0.36$); whereas nonsevere COVID+ patients were more likely to have a diagnosis of anosmia ($\chi^2[1] = 20.44$, $p < 0.0001$, $\varphi = 0.25$), ageusia ($\chi^2[1] = 11.24$, $p = 0.0008$, $\varphi = 0.24$), and headache ($\chi^2[1] = 40.00$, $p < 0.0001$). No patients were diagnosed with dizziness or acute cerebrovascular disease and were not considered in further analyses.

After controlling for demographic variables and history of comorbidities, the odds of developing severe COVID-19 in patients who displayed eCNSsx was 3.21 times higher than those who did not display eCNSsx (OR, 3.21; 95% CI, 2.93–3.53) (Table 3). Post hoc analyses of individual eCNSsx showed that diagnosis of anosmia (OR, 0.45; 95% CI, 0.23–0.79), ageusia (OR, 0.46; 95% CI, 0.21–0.89), and headache (OR, 0.63, 95% CI, 0.51–0.77) were associated with a reduced odds of developing severe COVID-19; whereas diagnosis of encephalopathy (OR, 14.38; 95% CI, 12.33–16.82) was associated with a greater odds of severe COVID-19

TABLE 3.
Hierarchal Logistic Regression Predicting Severe Coronavirus Disease 2019

	Step 1	Step 2	Step 3
Variable	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Age	1.05 (1.04–1.05)	1.05 (1.04–1.05)	1.05 (1.04–1.05)
Sex (reference group = female)	1.64 (1.53–1.75)	1.67 (1.56–1.79)	1.71 (1.59–1.83)
Race (reference group = White)			
Asian	1.27 (0.96–1.65)	1.30 (0.99–1.70)	1.32 (1.00–1.73)
Black	1.81 (1.65–1.98)	1.74 (1.59–1.90)	1.73 (1.58–1.90)
Other	0.80 (0.73–0.88)	0.86 (0.78–0.94)	0.91 (0.83–1.00)
Unknown	0.34 (0.28–0.42)	0.37 (0.30–0.46)	0.40 (0.32–0.50)
Hispanic (reference group = no)			
Yes	1.48 (1.35–1.62)	1.48 (1.35–1.62)	1.44 (1.31–1.57)
Unknown	0.86 (0.73–1.00)	0.91 (0.78–1.06)	0.91 (0.78–1.06)
With comorbidities		1.38 (1.28–1.49)	1.37 (1.27–1.48)
With early CNS symptoms			3.21 (2.93–3.53)
Akaike information criterion	22,650	22,580	22,029

aOR = adjusted odds ratio.
Results of the primary analysis, examining the odds of developing severe coronavirus disease 2019 based on the presence of any early CNS symptoms, after controlling for demographic variables and known comorbidities.

(Table 4). In further exploratory, post hoc analyses, there was a significant interaction between the diagnosis of encephalopathy and obesity (OR, 1.83; 95% CI, 1.06–3.41). No other encephalopathy and comorbidity interactions were significant (Table 4).

Finally, we explored the temporal relationship between diagnosis of COVID-19, duration until patients were classified as severe, and the latency of eCNSsx and severe disease. On average, patients met the classification of "severe" 0.73 days (SD = 4.15 d) from when they were diagnosed with COVID-19 based on PCR-based testing. **Table 5** displays the relationship between diagnosis of eCNSsx and development of severe COVID-19. Across all eCNSsx, the diagnosis of eCNSsx preceded the onset of severe COVID-19 by an average of 0.73 days (SD = 4.15 d). Notably, 5.1% of patients were diagnosed with encephalopathy prior to development of severe COVID-19 and 96.3% of the patients were diagnosed with encephalopathy before or concurrent with the development of severe COVID-19.

DISCUSSION

To our knowledge, this is the first study to systematically evaluate the relationship between eCNSsx and COVID-19 severity in a large, multicenter clinical sample. In this large study, we found that patients with eCNSsx had 3.21 times higher odds of developing severe COVID-19 compared with patients without eCNSsx. Consistent with prior literature, anosmia and ageusia were associated with a milder disease course (12). Encephalopathy specifically was associated with a much greater odds of severe COVID-19. This is consistent with prior studies linking increased morbidity and mortality to encephalopathic patients with COVID-19 (13). However, this is the first study, to our knowledge, that demonstrates an association of early encephalopathy and COVID severity.

In addition, our findings are aligned with the numerous other studies that found an association with age, gender, race, and ethnicity with COVID-19 severity (12). Similarly, we found that preexisting

TABLE 4.
Adjusted Odds Ratios of Severe Coronavirus Disease 2019 Based on Presence of Comorbidities and CNS Symptoms

Variable of Interest	Adjusted OR (95% CI)
Comorbidities	
Asthma	0.93 (0.80–1.08)
Hypoxemia	1.98 (1.51–2.60)
Diabetes	1.71 (1.54–2.60)
Hypertension	0.94 (0.86–1.04)
CKD	1.32 (1.15–1.51)
Obesity	1.12 (1.00–1.25)
Tobacco use	1.05 (0.90–1.22)
Immunodeficiency	1.03 (0.56–1.80)
COPD	1.06 (0.89–1.27)
Number of comorbidities	
0 comorbidities (reference)	
1–2 comorbidities	1.22 (1.13–1.33)
3+ comorbidities	1.84 (1.65–2.04)
Early CNS symptoms	
Anosmia	0.45 (0.23–0.79)
Ageusia	0.46 (0.21–0.89)
Headache	0.63 (0.51–0.77)
Ataxia	2.06 (0.22–17.47)
Encephalopathy	14.38 (12.33–16.82)
Encephalopathy × comorbidity interaction	
Encephalopathy × asthma	1.34 (0.69–2.81)
Encephalopathy × hypoxia	0.74 (0.24–3.25)
Encephalopathy × diabetes	0.45 (0.33–0.64)
Encephalopathy × hypertension	0.31 (0.23–0.42)
Encephalopathy × CKD	0.32 (0.21–0.48)
Encephalopathy × obesity	1.83 (1.06–3.41)
Encephalopathy × tobacco use	1.01 (0.56–1.91)
Encephalopathy × COPD	0.35 (0.21–0.59)

CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, OR = odds ratio.
OR predicting severe coronavirus disease 2019 by comorbidities after controlling for demographic variables, early CNS symptoms (eCNSsx) after controlling for demographic variables and presence of any comorbidity, and encephalopathy × comorbidity interaction after controlling for demographic variables, comorbidities, and eCNSsx.

comorbidities such as diabetes, CKD, and obesity were associated with a more severe disease course and displayed a compounding effect when more than one comorbidity was present (9).

It should be noted that the diagnostic term "encephalopathy" in our cohort was used as a clinical bridge for the multiple and varying degree of descriptors used to diagnose acute CNS impairment. Such descriptors included altered mental status, disorientation, impaired consciousness, and encephalopathy itself. To date, the neurologic literature has yet provided a reliable diagnostic algorithm to discriminate acute encephalopathy from other forms of acute brain dysfunction. Such a term is often used to define a broad range of neurologic alterations, presenting researchers with some diagnostic uncertainty. However, at present, it remains the best surrogate for acute brain dysfunction in COVID-19 and the literature alike.

Uniquely within our cohort, we show that 96.3% of our severe COVID-19 patients were diagnosed with encephalopathy either before or on the same day that they were classified as "severe" (i.e., required mechanical ventilation, admitted to ICU). Such a unimodal distribution of disease severity and encephalopathy suggests that acute brain dysfunction in severe COVID-19 is an early identifiable symptomology that predicts disease severity. Furthermore, its early recognition may aide clinician decision making in time to therapeutic intervention and escalation of care. Of interest, our sample also aimed to assess the presence of encephalopathy and comorbid interactions. Our data found that patients with clinical obesity and encephalopathy were 1.83 times more likely to develop severe COVID-19, suggesting a link between its pathogenesis and acute brain dysfunction. No other comorbidities were significant for such interaction. Current neuropathologic studies do not suggest that acute brain dysfunction in COVID-19 is related to direct neural invasion or hypoxic ischemic encephalopathy but rather microglial activation and neuronophagia from systemic inflammation (13). Such findings suggest that encephalopathy and its predictive nature of severe COVID may be a variable indicating the need for systemic anti-inflammatory therapy.

As with any retrospective analysis, limitations are inherent. The majority of our cohort was diagnosed with nonsevere COVID-19 similar to national trends.

TABLE 5.
Latency Between Severe Coronavirus Disease 2019 and Early CNS Symptoms Diagnosis

Early CNS Symptom	Mean (SD), d	−14 to −4 *n* (%)	−3 to −2 *n* (%)	−1 *n* (%)	0 *n* (%)	1 *n* (%)	2 to 3 *n* (%)	4+ *n* (%)
Anosmia	0.33 (0.88)	0 (0)	0 (0.0)	0 (0.0)	10 (83.3)	1 (8.3)	1 (8.3)	0 (0)
Ageusia	1.57 (7.93)	1 (7.1)	0 (0)	0 (0)	7 (50.0)	2 (14.3)	1 (7.1)	3 (21.4)
Headache	1.80 (4.47)	11 (2.8)	4 (1.0)	1 (0.3)	237 (59.7)	27 (6.8)	38 (9.6)	79 (19.9)
Ataxia	1.10 (2.98)	0 (0)	0 (0)	0 (0)	17 (81.0)	1 (4.8)	1 (4.8)	2 (9.5)
Encephalopathy	0.34 (2.60)	35 (1.4)	9 (0.4)	18 (0.7)	2,317 (91.2)	42 (1.7)	22 (0.9)	97 (3.8)

Negative numbers indicate early CNS symptoms diagnosed "prior" to classification of severe coronavirus disease 2019.

Twelve percent of our patient population was diagnosed with severe COVID-19, with the large majority (n = 2,317) diagnosed within 24 hours of hospital admission. This suggests that most patients sought emergent medical attention when symptoms were severe or life-threatening and multisystem *International Classification of Diseases* coding was at its highest. In concordance, eCNSsx and most notably encephalopathy followed a similar trend. Such findings suggest that reporting bias, especially for mild neurologic symptoms, may have led to under-coding of neurologic symptoms, potentially indicating there may be a higher proportion of patients who were encephalopathic earlier in the disease process. Analog findings were discovered early on when studying anosmia and dysgeusia where broad variations in frequency were found depending on methodology (14). Similarly, we cannot confirm the diagnostic criterion or medical decision-making process across the different sites, however, our partner sites were all large academic medical centers with high rates of COVID-19 and ICU COVID-19 capacity (15). Lastly, despite attempts to reduce limitations, selection bias toward those that could afford healthcare might skew the results to overinflate patients with more complicated presentation; however, most patients with severe COVID would likely have to seek medical attention, and this selection might be a larger consideration for mild or moderate severe acute respiratory syndrome coronavirus 2 infection. Although definitive conclusions cannot be drawn due to the observational nature of this study, such limitations are hypothesis generating in that early and abrupt recognition of encephalopathy in the outpatient and nonsevere COVID cohorts may predict progression to severe COVID-19. Such consideration should be further investigated prospectively.

At present, there is a coordinated effort in the scientific community to develop therapies for early COVID-19 (16). The identification of a subgroup of patients at higher risk of severe disease may help to redirect that effort to prevent disease progression in those patients. COVID+ patients with early onset or presenting symptoms of encephalopathy may need closer monitoring, especially early in the disease process.

1 *Department of Clinical and Health Psychology, University of Florida, Gainesville, FL.*

2 *Department of Neurology, UF College of Medicine, University of Florida, Gainesville, FL.*

3 *Department of Neurosurgery, UF College of Medicine, University of Florida, Gainesville, FL.*

4 *Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, FL.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Research reported in this publication was supported by the University of Florida Clinical and Translational Science Institute, which is supported in part by the National Institutes of Health, National Center for Advancing Translational Sciences under award number UL1TR001427.

The authors have disclosed that they do not have any potential conflicts of interest.

Address requests for reprints to: David E. Marra, PhD, Department of Clinical and Health Psychology, University of Florida, 1225 Center Drive, Gainesville, FL 32610. E-mail: dmarra3@phhp.ufl.edu

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Mao L, Jin H, Wang M, et al: Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; 77:683–690
2. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al: Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur Arch Otorhinolaryngol* 2020; 277:2251–2261
3. Whittaker A, Anson M, Harky A: Neurological manifestations of COVID-19: A systematic review and current update. *Acta Neurol Scand* 2020; 142:14–22
4. Yan CH, Faraji F, Prajapati DP, et al: Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol* 2020; 10:821–831
5. Garg RK, Paliwal VK, Gupta A: Encephalopathy in patients with COVID-19: A review. *J Med Virol* 2021; 93:206–222
6. Liotta EM, Batra A, Clark JR, et al: Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol* 2020; 7:2221–2230
7. Eskandar EN, Altschul DJ, de la Garza Ramos R, et al: Neurologic syndromes predict higher in-hospital mortality in COVID-19. *Neurology* 2021; 96:e1527–e1538
8. Shenkman E, Hurt M, Hogan W, et al: OneFlorida clinical research consortium: Linking a clinical and translational science institute with a community-based distributive medical education model. *Acad Med* 2018; 93:451–455
9. Tisminetzky M, Delude C, Hebert T, et al: Age, multiple chronic conditions, and COVID-19: A literature review. *J Gerontol A Biol Sci Med Sci* 2020 Dec 24. [online ahead of print]
10. Lauer SA, Grantz KH, Bi Q, et al: The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. *Ann Intern Med* 2020; 172:577–582
11. Wang D, Hu B, Hu C, et al: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; 323:1061–69
12. Wang Z, Zheutlin A, Kao YH, et al: Hospitalised COVID-19 patients of the Mount Sinai Health System: A retrospective observational study using the electronic medical records. *BMJ Open* 2020; 10:e040441
13. Thakur KT, Miller EH, Glendinning MD, et al: COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain* 2021 Apr 15. [online ahead of print]
14. Agyeman AA, Chin KL, Landersdorfer CB, et al: Smell and taste dysfunction in patients with COVID-19: A systematic review and meta-analysis. *Mayo Clin Proc* 2020; 95:1621–1631
15. Caspani M, Borter G: Dozens of Florida Hospitals Out of Available ICU Beds, State Data Shows. Reuters. 2020 Available at: https://www.reuters.com/article/us-health-coronavirus-usa-florida/dozens-of-florida-hospitals-out-of-available-icu-beds-state-data-shows-idUSKBN2482IS. Accessed April 26, 2021
16. Kim PS, Read SW, Fauci AS: Therapy for early COVID-19: A critical need. *JAMA* 2020; 324:2149–2150