PLOS ONE

RESEARCH ARTICLE

Altered mental status is a predictor of poor outcomes in COVID-19 patients: A cohort study

Abdallah S. Attia[1], Mohammad Hussein[1], Mohamed A. Aboueisha[1,2], Mahmoud Omar[1], Mohanad R. Youssef[1], Nicholas Mankowski[1], Michael Miller[1], Ruhul Munshi[1], Aubrey Swinford[1], Adam Kline[1], Therese Nguyen[1], Eman Toraih[1,3], Juan Duchesne[1], Emad Kandil[1]*

1 Department of Surgery, School of Medicine, Tulane University, New Orleans, Louisiana, United States of America, **2** Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Suez Canal University, Ismailia, Egypt, **3** Genetics Unit, Department of Histology and Cell Biology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

* ekandil@tulane.edu

OPEN ACCESS

Citation: Attia AS, Hussein M, Aboueisha MA, Omar M, Youssef MR, Mankowski N, et al. (2021) Altered mental status is a predictor of poor outcomes in COVID-19 patients: A cohort study. PLoS ONE 16(10): e0258095. https://doi.org/10.1371/journal.pone.0258095

Editor: Tai-Heng Chen, Kaohsuing Medical University Hospital, TAIWAN

Received: January 27, 2021

Accepted: September 19, 2021

Published: October 5, 2021

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0258095

Data Availability Statement: All relevant data are within the manuscript.

Funding: The author(s) received no specific funding for this work.

Abstract

Introduction

Several studies have described typical clinical manifestations, including fever, cough, diarrhea, and fatigue with COVID-19 infection. However, there are limited data on the association between the presence of neurological manifestations on hospital admission, disease severity, and outcomes. We sought to investigate this correlation to help understand the disease burden.

Methods

We delivered a multi-center retrospective study of positive laboratory-confirmed COVID-19 patients. Clinical presentation, laboratory values, complications, and outcomes data were reported. Our findings of interest were Intensive Care Unit (ICU) admission, intubation, mechanical ventilation, and in-hospital mortality.

Results

A total of 502 patients with a mean age of 60.83 ± 15.5 years, of them 71 patients (14.14%) presented with altered mental status, these patients showed higher odds of ICU admission (OR = 2.06, 95%CI = 1.18 to 3.59, $p = 0.01$), mechanical ventilation (OR = 3.28, 95%CI = 1.86 to 5.78, $p < 0.001$), prolonged (>4 days) mechanical ventilation (OR = 4.35, 95%CI = 1.89 to 10, $p = 0.001$), acute kidney injury (OR = 2.18, 95%CI = 1.28 to 3.74, $p = 0.004$), and mortality (HR = 2.82, 95%CI = 1.49 to 5.29, $p = 0.01$).

Conclusion

This cohort study found that neurological presentations are associated with higher odds of adverse events. When examining patients with neurological manifestations, clinicians

Competing interests: The authors have declared that no competing interests exist.

should suspect COVID-19 to avoid delayed diagnosis or misdiagnosis and lose the chance to treat and prevent further transmission.

Introduction

Since the Spanish flu pandemic in 1918, humankind hasn't encountered such an overwhelming health crisis created by the novel 2019 coronavirus disease (COVID-19) pandemic [1]. As of August 2, 2020, the World Health Organization (WHO) reports that 680,894 people have died around the world, spanning different countries, ethnicities, religions, and socioeconomic class. Furthermore, the Emergency Committee on COVID-19 unanimously admitted that the outbreak still poses a public health emergency of international concern [2].

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially thought to primarily infect the respiratory system with dyspnea, cough, expectoration, and chest pain being common presenting symptoms [3]. However, as the pandemic continues, it is has been shown that the virus affects a wide range of organ systems, including the gastrointestinal, hepatic, renal, and cardiovascular systems. Well-documented extrapulmonary findings in COVID-19 patients include diarrhea, nausea, vomiting, elevated liver enzymes, kidney dysfunction, elevated troponin and CK-MB, systolic dysfunction, and heart failure, especially those who developed a severe and critical illness [3–9].

Some articles have illustrated symptoms suggestive of potential nervous system involvement with many studies demonstrating anosmia, ageusia, dizziness, seizure, altered mental status (AMS), myalgia, headache, syncope, somnolence, and coma in COVID-19 patients [7–9, 10]. Neuropsychiatric manifestations, such as anxiety, depression, insomnia, and psychosis, are reported as well [7, 10]. Case reports and case series have reported para-infectious conditions including Guillain-Barre syndrome and ataxia [11]. However, there is limited data available describing neurological symptoms as presenting manifestations among COVID-19 patients. The purpose of this multi-center retrospective cohort study was to investigate whether presenting with neurological symptoms is a predictor of poor health outcomes and adverse events in COVID-19 positive patients.

Methods

Study design and population

This is a multi-center retrospective cohort study that was performed after acquiring Tulane University Institutional Review Board (IRB) approval. The patient data were collected on COVID-19 confirmed positive patients, who were admitted from March 20, 2020, to May 10, 2020, to Tulane Medical Center (TMC) and University Medical Center (UMC) in New Orleans, LA. The patient data was collected using Research Electronic Data Capture (REDCap) hosted at Tulane University Medical School. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture and audit trails for tracking data manipulation and export procedures [12]. Patients were divided into two groups: with and without altered mental status (AMS) which encompasses confusion, amnesia, loss of alertness, disorientation, defects in judgment or thought, unusual or strange behavior, poor regulation of emotions, and disruptions in perception, psychomotor skills, and behavior. Patients were diagnosed with AMS on admission by the attending physician and patients were not on any sedative agents at the time of diagnosis.

Variables

Demographics, presenting symptoms, comorbidities, clinical notes, laboratory values, and health outcomes were extracted from the electronic medical records using a standardized data collection. Patient orientation and mental state were determined using Glasgow Coma Scale (GCS), patients with decreased GCS were considered to have Altered mental status. The severity of the disease was determined by two scoring systems: CURB-65 and Quick Sequential Organ Failure Assessment (qSOFA). The CURB-65 score is based on the presence of confusion, blood urea nitrogen level >19 mg/dL (>7 mmol/L), respiratory rate ≥30, blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg), and age ≥65 years [13]. (2) The qSOFA score is based on a GCS <15, respiratory rate ≥22, and systolic blood pressure ≤100 [14].

Outcomes

A comparison between patients with and without AMS was performed. Outcome measures investigated included disease course, Intensive Care Unit (ICU) admission, intubation, unplanned reintubation, mechanical ventilation, duration of mechanical ventilation, prolonged mechanical ventilation, ARDS, bacteremia, sepsis, acute kidney injury, length of hospital stay, and mortality.

Statistical analysis

Data management was performed using SAS v9.4, while SPSS v26.0 was used for statistical analysis. Chi-square and Fisher's Exact tests were applied for categorical variables. Student's t and Mann-Whitney U tests were used for continuous variables. The two-sided *p*-value was set to be significant at <0.05. Multiple regression analysis was iterated using binary logistic regression models for all outcomes and cox hazard proportionate regression model for survival, adjusted by age, sex, obesity, and neuropsychiatric comorbidity.

Results

Demographics, comorbidities, and symptoms

We included a total of 502 COVID-19 confirmed positive patients with a mean age of 60.83 ± 15.5 years, and 238 patients (47.4%) were males. Their mean body mass index (BMI) was 33.32 ± 8.54 Kg/m^2, with 57.2% being obese having BMI >30 Kg/m^2 and 24.7% being overweight with a BMI >25 kg/m^2. Most participants were African Americans (74.7%). On admission, 37 (7.37%) participants were classified as asymptomatic, 71 patients (14.14%) presented with AMS including 25 patients without any other manifestations, and 394 (78.48%) presented with other non-specific, respiratory, and gastrointestinal symptoms without neuropsychiatric symptoms, **Fig 1**. Patients with AMS were significantly older (68.61 ± 16.36 years versus 59.56 ± 15.01 years, p <0.001) and had lower BMI (30.91 ± 8.36 Kg/m^2 versus 33.83 ± 8.50 Kg/m^2, p = 0.021). Patients with AMS were less likely to be African American (66.2% versus 76.1%, p = 0.023), obese (45.1% versus 59.2%, p = 0.028), and have shortness of breath on admission (33.8% versus 58.2%, p < 0.001), **Table 1**.

Clinical assessment

Patients with AMS had a higher qSOFA score (1.40 ± 0.76 versus 0.58 ± 0.61, p <0.001), CURB-65 score (2.63 ± 1.07 versus 1.22 ± 1.00, p <0.001) and lower GCS (9.41 ± 4.0815.00 ± 0.00, p<0.001) compared to non-AMS cohorts, **Table 1**.

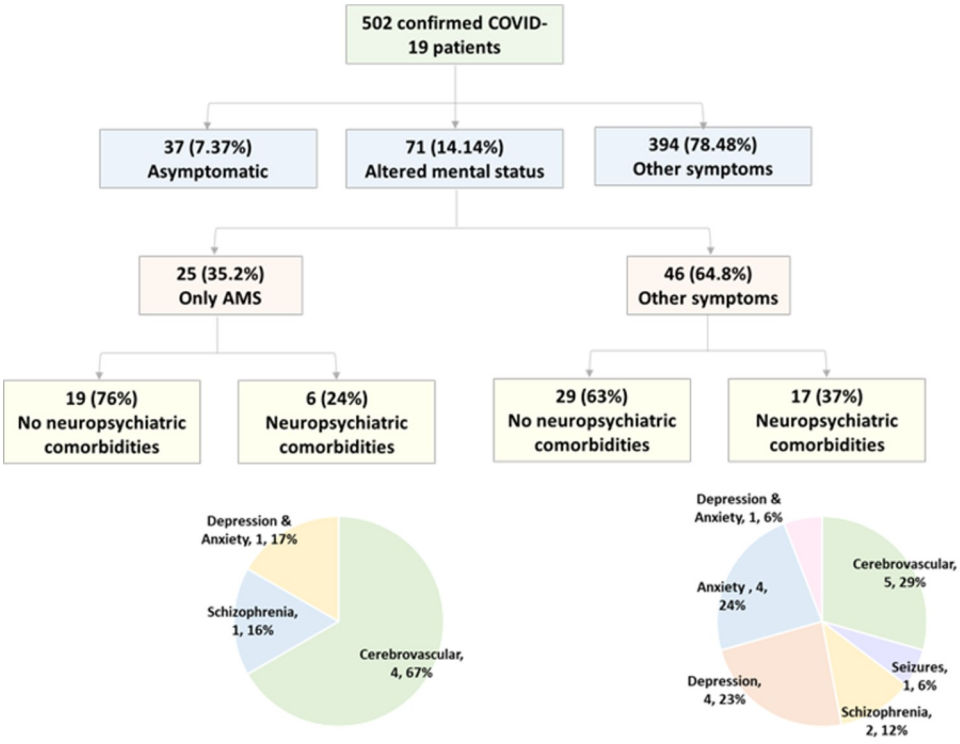

Fig 1. Hierarchical classification of patients according to neuropsychiatric symptoms and comorbidities.

https://doi.org/10.1371/journal.pone.0258095.g001

Laboratory findings

Patients presented with AMS had a lower PaO_2/FiO_2 (192.89 ± 114.26 versus 265.26 ± 103.25, $p = 0.003$) and higher white blood cell count (9.69 ± 6.03 versus 7.85 ± 5.26, $p = 0.013$), neutrophil-to-lymphocyte ratio (10.78 ± 9.38 versus 7.18 ± 9.76, $p = 0.007$), blood urea nitrogen (31.15 ± 19.23 versus 25.01 ± 20.39, $p = 0.02$), and C-reactive protein (CRP) (93.61 ± 81.27 versus 32.36 ± 47.69, $p = 0.001$) compared to patients without AMS, Table 1.

Adverse events

Patients presented with AMS showed worse outcomes compared to patients without AMS. Presenting with AMS was associated with higher rates of ICU admission (42.3% versus 27.7%, $p = 0.017$), intubation (45.1% versus 27%, $p = 0.003$), mechanical ventilation (47.9% versus 24.6%, $p < 0.001$), unplanned reintubation (35.3% versus 9.5%, $p = 0.012$), sepsis (23.9% versus 13.5%, $p = 0.03$), and acute kidney injury (N = 26, 36.6% versus N = 90, 20.9%, $p = 0.006$), Table 2.

Mortality and length of stay

Patients presented with AMS had a higher rate of mortality (29.6% versus 11.6%, $p < 0.001$), earlier death (9.05 ± 5.08 days versus 15.07 ± 9.27, $p = 0.007$), and longer duration on ventilators (4.63 ± 6.08 days versus 1.43 ± 3.51 days, $p < 0.001$), Table 2.

Predictors risk factor for poor outcomes in patients with AMS

The multiple regression analysis was adjusted for age, sex, obesity, and neuropsychiatric comorbidities. This analysis revealed that patients presented with AMS had higher odds of

Table 1. Characteristics of COVID-19 patients at admission.

Characteristics		Non-AMS (n = 431)	AMS (n = 71)	P value
Demographic data				
Age	Mean ± SD	59.56 ± 15.01	68.61 ± 16.36	<**0.001**
	18–49 years	97 (22.7)	12 (17.1)	<**0.001**
	50–64 years	172 (40.2)	12 (17.1)	
	≥ 65 years	159 (37.1)	46 (65.7)	
Sex	Female	228 (53.1)	33 (47.1)	0.36
	Male	201 (46.9)	37 (52.9)	
Race	African American	328 (76.1)	47 (66.2)	**0.023**
	White	72 (16.7)	12 (16.9)	
	Not Reported	31 (7.2)	12 (16.9)	
BMI, kg/m^2	Mean ± SD	33.83 ± 8.50	30.91 ± 8.36	**0.021**
Smoking	None	302 (70.1)	44 (62)	0.26
	Past smoker	90 (20.9)	21 (29.6)	
	Current smoker	39 (9)	6 (8.5)	
Chief complaints				
Asymptomatic	Asymptomatic	37 (8.6%)	NA	NA
Non-specific	Fever	97 (22.5)	11 (15.5)	0.21
	Fatigue/weakness	31 (7.2)	1 (1.4)	0.06
	Myalgia/FLS	28 (6.5)	5 (7)	0.79
	Headache	6 (1.4)	1 (1.4)	0.99
Respiratory symptoms	Shortness of breath	251 (58.2)	24 (33.8)	<**0.001**
	Cough	104 (24.1)	11 (15.5)	0.12
	Chest pain	13 (3)	0 (0)	0.23
GIT symptoms	Nausea, vomiting, diarrhea	28 (6.5)	3 (4.2)	0.60
Comorbidities				
Neuropsychiatric	Overall	99 (23)	23 (32.4)	0.10
	Cerebrovascular disease	29 (6.7)	9 (12.7)	0.09
	Seizures	6 (1.4)	1 (1.4)	0.99
	Mood disorders	43 (10)	7 (9.9)	0.97
	Anxiety disorder	24 (5.6)	6 (8.5)	0.41
	Schizophrenia	10 (2.3)	3 (4.2)	0.40
Other comorbidities	Overall	378 (87.7)	64 (90.1)	0.69
	Obesity	255 (59.2)	32 (45.1)	**0.028**
	Hypertension	303 (70.3)	54 (76.1)	0.39
	Diabetes	185 (42.9)	26 (36.6)	0.36
	Chronic heart failure	39 (9)	11 (15.5)	0.13
	Arrhythmia	40 (9.3)	8 (11.3)	0.66
	Coronary artery disease	39 (9)	10 (14.1)	0.20
	Asthma	66 (15.3)	6 (8.5)	0.15
	COPD	30 (7)	6 (8.5)	0.62
	Chronic kidney disease	63 (14.6)	13 (18.3)	0.47
	Cancer	46 (10.7)	9 (12.7)	0.68
Clinical assessment				
Severity	qSOFA score	0.58 ± 0.61	1.40 ± 0.76	<**0.001**
	CURB65 score	1.22 ± 1.00	2.63 ± 1.07	<**0.001**
Orientation	Glasgow coma score	15.00 ± 0.00	9.41 ± 4.08	<**0.001**

(*Continued*)

Table 1. (Continued)

Characteristics		Non-AMS (n = 431)	AMS (n = 71)	P value
Vital signs	Temperature (F)	99.65 ± 1.72	98.75 ± 1.67	**<0.001**
	Pulse rate	91.21 ± 19.06	83.18 ± 21.20	**0.002**
	Systolic blood pressure	126.34 ± 20.18	122.84 ± 24.56	0.21
	Diastolic blood pressure	74.33 ± 14.82	70.07 ± 15.77	**0.033**
	Mean arterial pressure	101.10 ± 18.08	100.54 ± 21.13	0.82
	Respiratory rate	22.25 ± 7.39	21.39 ± 6.16	0.37
ABG findings	SaO_2	92.87 ± 7.88	94.26 ± 7.37	0.18
	pH respiratory	7.26 ± 1.02	7.40 ± 0.07	0.45
	$PaCO_2$	39.27 ± 13.99	38.17 ± 9.62	0.67
	PaO_2	86.44 ± 60.70	99.33 ± 99.46	0.34
	Anion gap	11.73 ± 10.53	12.90 ± 3.55	0.56
	Lactic acid	54.82 ± 108.90	33.87 ± 85.16	0.66
	HCO_3	24.96 ± 3.19	22.91 ± 4.94	**0.017**
	FiO_2 (%)	33.59 ± 24.87	58.57 ± 33.08	**<0.001**
	PaO_2/FiO_2 ratio	265.26 ± 103.25	192.89 ± 114.26	**0.003**
Laboratory findings				
Complete blood picture	White blood cells ($x10^9$/L)	7.85 ± 5.26	9.69 ± 6.03	**0.013**
	Hemoglobin (g/dl)	12.11 ± 2.08	11.98 ± 2.07	0.66
	Hematocrit (%)	36.32 ± 5.91	35.95 ± 5.95	0.69
	Platelet count ($x10^9$/L)	237.75 ± 100.14	239.22 ± 126.82	0.92
	Neutrophil count ($x10^9$/L)	6.58 ± 8.78	8.85 ± 11.16	0.07
	Lymphocyte count (x109/L)	1.34 ± 1.94	1.08 ± 0.77	0.29
	Neutrophil lymphocyte ratio	7.18 ± 9.76	10.78 ± 9.38	**0.007**
Electrolytes	Serum sodium (mmol/L)	209.29 ± 937.39	138.85 ± 5.20	0.59
	Serum potassium (mmol/L)	4.09 ± 1.14	4.06 ± 0.65	0.84
	Serum chloride (mmol/L)	101.46 ± 5.24	101.75 ± 14.86	0.82
	Calcium corrected (mmol/L)	9.02 ± 0.67	8.90 ± 0.80	0.18
Glycemic profile	Random blood sugar (mg/dl)	144.47 ± 84.51	158.75 ± 97.36	0.22
	HbA1c (%)	7.94 ± 3.05	5.70 ± 0.00	0.49
Renal function test	Blood urea nitrogen (mg/dl)	25.01 ± 20.39	31.15 ± 19.23	**0.025**
	Serum creatinine (mg/dl)	1.74 ± 2.00	2.03 ± 2.19	0.28
Liver function test	Total protein (g/dl)	6.98 ± 0.74	6.88 ± 0.55	0.48
	Albumin (g/dl)	3.29 ± 0.55	3.06 ± 0.67	**0.017**
	Bilirubin (mg/dl)	0.61 ± 0.45	0.69 ± 0.49	0.35
	Alkaline phosphatase (U/L)	75.41 ± 44.18	74.27 ± 33.48	0.90
	AST (U/L)	48.16 ± 33.70	54.27 ± 43.07	0.41
	ALT (U/L)	35.52 ± 29.73	33.43 ± 26.72	0.73
Cardiac marker	Troponin (ng/ml)	3.63 ± 16.61	0.78 ± 1.55	0.62
Inflammatory markers	C-reactive protein (mg/dl)	32.36 ± 47.69	93.61 ± 81.27	**0.001**
	Procalcitonin (ng/ml)	11.64 ± 66.58	0.30 ± 0.30	0.50
	Ferritin (ng/ml)	989.76 ± 1,922.35	1,428.71 ± 2,825.35	0.38

AMS: altered mental status, FLS: Flu-like symptoms, GIT: gastrointestinal tract, NA: not applicable.

Data are presented as mean and standard deviation or frequency and percentage. BMI: body mass index. SaO2: oxygen saturation, PaO2: partial pressure of oxygen, PaCO2: partial pressure of carbon dioxide, HCO3: bicarbonate, FiO2: Fraction of inspired oxygen, AST: Aspartate transaminase, ALT: alanine transaminase, HbA1c: glycosylated hemoglobin. Chi-square, Fisher's Exact, Student's t, or Mann-Whitney U tests were used. *P*-value at <0.05 was considered significant.

https://doi.org/10.1371/journal.pone.0258095.t001

Table 2. Outcomes of COVID-19 patients with and without altered mental status.

Characteristics		Non-AMS (n = 431)	AMS (n = 71)	*P*-value
		N (%) or M±SD	N (%) or M±SD	
Hospital admission	Floor	312(72.3)	41 (57.7)	**0.017**
	ICU	119 (27.7)	30 (42.3)	
Procedures	Mechanical ventilation	106 (24.6)	34 (47.9)	**<0.001**
	Require intubation	115 (27)	32 (45.1)	**0.003**
	Extubation*	84 (73)	17 (53.1)	**0.032**
Develop complications	Negative	215 (49.9)	31 (43.7)	0.37
	Positive	216 (50.1)	40 (56.3)	
Type of complications	ARDS	139 (32.3)	21 (29.6)	0.68
	Unplanned reintubation**	8 (9.5)	6 (35.3)	**0.012**
	Sepsis	58 (13.5)	17 (23.9)	**0.030**
	Bacteremia	32 (7.4)	2 (2.8)	0.20
	Acute kidney injury	90 (20.9)	26 (36.6)	**0.006**
Mortality	Alive	381 (88.4)	50 (70.4)	**<0.001**
	Dead	50 (11.6)	21 (29.6)	
Death location***	Floor	3 (7)	3 (14.3)	0.38
	ICU	40 (93)	18 (85.7)	
Days to event	Renal failure	2.44 ± 3.19	2.67 ± 4.62	2.44
	ARDS	1.97 ± 2.10	0.60 ± 1.34	1.97
	Sepsis	1.19 ± 2.14	0.75 ± 1.50	1.19
	Extubation	8.93 ± 5.47	8.67 ± 7.30	0.90
	Death	15.07 ± 9.27	9.05 ± 5.08	**0.007**
Ventilation days	Overall	1.43 ± 3.51	4.63 ± 6.08	**<0.001**
	Discharged	0.90 ± 2.78	2.82 ± 6.88	**0.017**
	Deceased	6.33 ± 5.38	6.83 ± 4.12	0.76
Total LOS	Overall	12.24 ± 11.11	10.89 ± 9.79	0.40
	Discharged	11.89 ± 11.29	12.09 ± 11.84	0.92
	Deceased	14.81 ± 9.45	9.05 ± 5.08	**0.011**
ICU LOS	Overall	9.38 ± 7.60	8.46 ± 5.97	0.56
	Discharged	7.96 ± 6.52	10.29 ± 9.01	0.39
	Deceased	12.27 ± 8.84	7.86 ± 4.70	**0.040**

Data are presented as mean and standard deviation (M±SD) or frequency and percentage between parentheses.

*Percentage among intubated patients

**Percentage among extubated patients

*** data for the death location for 7 patients were missing.

https://doi.org/10.1371/journal.pone.0258095.t002

ICU admission (OR = 2.06, 95% CI = 1.18 to 3.59, $p = 0.010$), intubation (OR = 2.53, 95% CI = 1.44 to 4.43, $p = 0.001$), mechanical ventilation (OR = 3.28, 95% CI = 1.86 to 5.78, $p < 0.001$), prolonged (>4 days) ventilation (OR = 4.35, 95% CI = 1.86 to 10, $p = 0.001$), sepsis (OR = 2.02, 95% CI = 1.10 to 3.73, $p = 0.024$), acute kidney injury (OR = 2.18, 95% CI = 1.28 to 3.74, $p = 0.004$), and mortality (HR = 2.81, 95% CI = 1.49 to 5.29, $p = 0.001$), Fig 2.

Discussion

The COVID-19 pandemic has been a serious health emergency and has caused an unprecedented international disaster while creating damaging social, economic, and political consequences that will likely have devastating long-term effects. Following disease-control

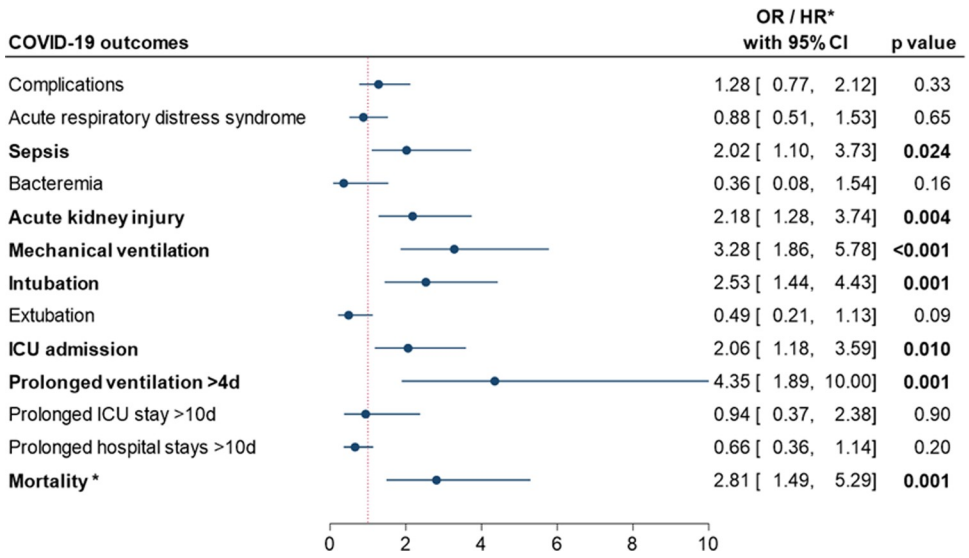

Fig 2. Impact of altered mental status as a predictor risk factor for poor outcomes. Multiple regression analysis was iterated using binary logistic regression models for all outcomes and cox hazard proportionate regression model for survival, adjusted by age, sex, obesity, and neuropsychiatric comorbidity. Results are reported as odds ratio (OR) for all outcomes or hazard ratio (HR*) for survival.

https://doi.org/10.1371/journal.pone.0258095.g002

guidelines, identifying risk factors, and recognizing different manifestations of COVID-19 infection is critical to deterring the spread and progression to severe disease. In response to this crisis, we conducted a retrospective cohort study on 502 hospitalized laboratory-confirmed COVID-19 patients to identify the outcomes associated with neurological symptoms, specifically AMS.

Angiotensin-converting enzyme 2 (ACE2) is the host functional receptor recognized by viral protein (spike) and allows the SARS-CoV-2 to enter the cell [15]. It is documented that SARS-CoV-2 has a higher affinity for ACE2 compared to its predecessor, SARS-CoV, explaining the higher rates of transmission. Due to the high presence of ACE2 on type II alveolar epithelial cells, the lung is the primary target and most vulnerable organ. However, the expression of ACE2 is ubiquitous, presenting in other multiple human tissues, including adipose tissue and nervous system [7, 16–18]. Due to increased expression in ACE2 in adipose tissue, obese individuals, could develop an explosive systemic inflammatory response, possibly contributing to the development of a more severe form of the disease [19]. Expression of ACE2 on glial cells, neurons, and capillary endothelial cells suggests that SARS-CoV-2 may invade the central nervous system (CNS) via direct invasion or cerebrovascular endothelium [7, 20–22].

Paniz-Mondolfi et al. reported the presence of SARS-CoV-2 in brain tissue from the post-mortem examination of a COVID-19 patient by implementing a transmission electron microscope. The viral particles were detected in the frontal lobe and matched the structural characteristics of SARS-CoV-2. Notably, these viral particles were found in the small vesicles of endothelial cells, which supports CNS invasion via hematogenous pathways may be a cause of the rapid progression of neurological symptoms [23]. Additionally, SARS-CoV-2 was identified in the cerebrospinal fluid (CSF) via polymerase chain reaction (PCR) in a male patient suffering from impaired consciousness and transient generalized seizures, with typical meningitis and encephalitis characteristics shown on the magnetic resonance imaging (MRI). Interestingly, this case presented with negative PCR results in the nasopharyngeal swab, which indicated that CNS invasion might have occurred in the early phase of COVID-19 infection [24]. It is also suggested

that direct invasion into the neuronal cells and retrograde transport from the olfactory bulb may be the pathophysiology of anosmia experienced by some COVID-19 patients [22, 25].

To our knowledge, this is the first cohort study comparing outcomes between COVID-19 patients with and without neurologic symptoms, specifically AMS, while utilizing validated scoring systems (GCS, CURB-65, and qSOFA). Our initial univariate analysis showed that 14.14% of the COVID-19 patients presented to the hospital with AMS. These patients had higher rates of developing adverse events such as ICU admission, intubation, mechanical ventilation, prolonged ventilation, extended hospital stay, and mortality. But they had a lower rate of shortness of breath which could be explained due to the decreased reporting of symptoms with patients with AMS [26]. Out of the patients presenting with AMS in our cohort, 25 (35.2%) presented with no other symptoms. Mao et al. also reported that neurological symptoms, including impaired consciousness, occurred early in the disease course, sometimes preceding typical respiratory symptoms [7]. This suggests that neurological symptoms, such as AMS, may be signs of impending clinical decline in the early stages of COVID-19.

The patients with AMS presented with comparatively more severe disease, shown by the significantly higher CURB-65 and qSOFA scores at the time of admission. Additionally, patients with AMS presented with significantly higher neutrophil-to-lymphocyte ratio and CRP, which are risk factors of poor health outcomes and possible predictors of severe disease [27–30]. However, it cannot be definitively determined if AMS is a result of a more severe disease or that neurological involvement, manifesting as AMS, is causing more severe features of COVID-19.

Older age, obesity, and being African American are all associated with poor health outcomes in COVID-19 patients [19, 31–34]. The prevalence of obese patients in our study was 57% which is higher than Louisiana's average (35%) [35]. It should be acknowledged that the AMS cohort has a significantly older average age. However, when adjusted for age, AMS remained more associated with poor health outcomes, **Fig 2**. Notably, patients with AMS were less likely to be African American or have obesity, which strengthens the argument that AMS may be an independent risk factor for poor health outcomes in COVID-19 patients. But we were unable to explain the reason why.

There are many established etiologies of AMS, including neurologic, toxicologic, trauma, psychiatric, and infectious [34]. Neuropsychiatric comorbidities could predispose patients to develop AMS. In our cohort, there was no significant difference in the prevalence of neuropsychiatric comorbidities between patients with and without AMS. Additionally, AMS was remained associated with poor health outcomes when the analysis was adjusted for neuropsychiatric comorbidities, **Fig 2**. Dehydration is also associated with developing AMS, especially in elderly patients [36]. Diarrhea and vomiting are possible causes of dehydration, and there was no significant difference in the prevalence of these symptoms between the study groups. Additionally, AMS secondary to hospital-induced delirium can be ruled out, since all these patients presented with AMS at admission.

Further studies are needed to determine if presenting with only AMS is also associated with poor health outcomes, and why they are presented less in obese and African American patients, which may further strengthen the argument that it should be considered an independent risk factor for poor health outcomes. Limiting data analysis to data upon admission is a potential limitation, which makes it prone to missing data such as CT-scans, MRI, and CSF analysis, which are vital in identifying brain injury and signs of neurological invasion of SAR-CoV-2.

Author Contributions

Conceptualization: Abdallah S. Attia, Mohammad Hussein, Mohanad R. Youssef, Emad Kandil.

Data curation: Abdallah S. Attia, Mohammad Hussein, Mahmoud Omar, Mohanad R. Youssef, Aubrey Swinford, Adam Kline, Therese Nguyen, Emad Kandil.

Formal analysis: Abdallah S. Attia, Mohammad Hussein, Eman Toraih.

Funding acquisition: Abdallah S. Attia.

Investigation: Abdallah S. Attia, Mohanad R. Youssef, Eman Toraih.

Methodology: Abdallah S. Attia, Mohammad Hussein, Eman Toraih, Emad Kandil.

Project administration: Abdallah S. Attia.

Resources: Abdallah S. Attia, Eman Toraih, Emad Kandil.

Software: Eman Toraih.

Supervision: Eman Toraih, Juan Duchesne, Emad Kandil.

Validation: Eman Toraih.

Visualization: Abdallah S. Attia, Mohamed A. Aboueisha.

Writing – original draft: Abdallah S. Attia, Mohamed A. Aboueisha, Mahmoud Omar, Nicholas Mankowski.

Writing – review & editing: Abdallah S. Attia, Mohamed A. Aboueisha, Mahmoud Omar, Nicholas Mankowski, Michael Miller, Ruhul Munshi, Aubrey Swinford, Adam Kline, Therese Nguyen, Eman Toraih, Juan Duchesne, Emad Kandil.

References

1. Taubenberger JK, Morens DM. Influenza revisited. Emerg Infect Dis 2006; 12(1):1–2. https://doi.org/10.3201/eid1201.051442 [published Online First: 2006/04/14]. PMID: 16610160
2. Organization WH. Novel Coronavirus Disease 2020 [updated August 2nd]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
3. Li LQ, Huang T, Wang YQ, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020; 92(6):577–83. https://doi.org/10.1002/jmv.25757 [published Online First: 2020/03/13]. PMID: 32162702
4. Youssef M, M HH, Attia AS, et al. COVID-19 and liver dysfunction: A systematic review and meta-analysis of retrospective studies. J Med Virol 2020 https://doi.org/10.1002/jmv.26055 [published Online First: 2020/05/24]. PMID: 32445489
5. Zou F, Qian Z, Wang Y, et al. Cardiac Injury and COVID-19: A Systematic Review and Meta-Analysis. CJC Open 2020 https://doi.org/10.1016/j.cjco.2020.06.010 PMID: 32838255
6. Batlle D, Soler MJ, Sparks MA, et al. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. J Am Soc Nephrol 2020; 31(7):1380–83. https://doi.org/10.1681/ASN.2020040419 [published Online First: 2020/05/06]. PMID: 32366514
7. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurology 2020; 77(6):683–90. https://doi.org/10.1001/jamaneurol.2020.1127 PMID: 32275288
8. Chen L, Liu HG, Liu W, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2020; 43(3):203–08. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.03.013 [published Online First: 2020/03/14]. PMID: 32164089
9. 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(11):1061–69. https://doi.org/10.1001/jama.2020.1585 PMID: 32031570
10. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology 2020 https://doi.org/10.1212/WNL.0000000000009937 [published Online First: 2020/06/03]. PMID: 32482845

11. Zhao H, Shen D, Zhou H, et al. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020; 19(5):383–84. https://doi.org/10.1016/S1474-4422(20)30109-5 [published Online First: 2020/04/05]. PMID: 32246917

12. Patridge EF, Bardyn TP. Research Electronic Data Capture (REDCap). J Med Libr Assoc 2018; 106 (1):142–44. https://doi.org/10.5195/jmla.2018.319 [published Online First: 2018/01/02]

13. Nguyen Y, Corre F, Honsel V, et al. Applicability of the CURB-65 pneumonia severity score for outpatient treatment of COVID-19. J Infect 2020:S0163-4453(20)30330-3. https://doi.org/10.1016/j.jinf.2020.05.049 PMID: 32474039

14. Liu S, Yao N, Qiu Y, et al. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Am J Emerg Med 2020 https://doi.org/10.1016/j.ajem.2020.07.019 PMID: 33142178

15. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181(2):271-80.e8. https://doi.org/10.1016/j.cell.2020.02.052 [published Online First: 2020/03/07]. PMID: 32142651

16. Pinheiro TA, Barcala-Jorge AS, Andrade JMO, et al. Obesity and malnutrition similarly alter the renin-angiotensin system and inflammation in mice and human adipose. The Journal of nutritional biochemistry 2017; 48:74–82. https://doi.org/10.1016/j.jnutbio.2017.06.008 [published Online First: 2017/08/06]. PMID: 28779634

17. Frantz EDC, Giori IG, Machado MV, et al. High, but not low, exercise volume shifts the balance of renin-angiotensin system toward ACE2/Mas receptor axis in skeletal muscle in obese rats. American journal of physiology Endocrinology and metabolism 2017; 313(4):E473–e82. https://doi.org/10.1152/ajpendo.00078.2017 [published Online First: 2017/07/07]. PMID: 28679623

18. Zhang Y, Somers KR, Becari C, et al. Comparative Expression of Renin-Angiotensin Pathway Proteins in Visceral Versus Subcutaneous Fat. 2018; 9(1370) https://doi.org/10.3389/fphys.2018.01370 PMID: 30364113

19. Tamara A, Tahapary DL. Obesity as a predictor for a poor prognosis of COVID-19: A systematic review. Diabetes & metabolic syndrome 2020; 14(4):655–59. https://doi.org/10.1016/j.dsx.2020.05.020 [published Online First: 2020/05/22]. PMID: 32438328

20. Aghagoli G, Gallo Marin B, Katchur NJ, et al. Neurological Involvement in COVID-19 and Potential Mechanisms: A Review. Neurocritical care 2020:1–10. https://doi.org/10.1007/s12028-020-01049-4 [published Online First: 2020/07/15]. PMID: 32661794

21. Whittaker A, Anson M, Harky A. Neurological Manifestations of COVID-19: A systematic review and current update. 2020; 142(1):14–22. https://doi.org/10.1111/ane.13266 PMID: 32412088

22. Baig AM, Khaleeq A, Ali U, et al. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS chemical neuroscience 2020; 11(7):995–98. https://doi.org/10.1021/acschemneuro.0c00122 [published Online First: 2020/03/14]. PMID: 32167747

23. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 2020; 92(7):699–702. https://doi.org/10.1002/jmv.25915 [published Online First: 2020/04/22]. PMID: 32314810

24. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 2020; 94:55–58. https://doi.org/10.1016/j.ijid.2020.03.062 [published Online First: 2020/04/07]. PMID: 32251791

25. Giacomelli A, Pezzati L, Conti F, et al. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Clinical Infectious Diseases 2020; 71(15):889–90. https://doi.org/10.1093/cid/ciaa330 %J Clinical Infectious Diseases. PMID: 32215618

26. Han JH, Bryce SN, Ely EW, et al. The effect of cognitive impairment on the accuracy of the presenting complaint and discharge instruction comprehension in older emergency department patients. Annals of emergency medicine 2011; 57(6):662-71.e2. https://doi.org/10.1016/j.annemergmed.2010.12.002 [published Online First: 2011/01/29]. PMID: 21272958

27. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology 2020; 127:104370–70. https://doi.org/10.1016/j.jcv.2020.104370 PMID: 32344321

28. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect 2020; 50(4):332–34. https://doi.org/10.1016/j.medmal.2020.03.007 [published Online First: 2020/03/31]. PMID: 32243911

29. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020; 81(1):e6–e12. https://doi.org/10.1016/j.jinf.2020.04.002 [published Online First: 2020/04/14]. PMID: 32283162

30. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. 2020; 92(7):856–62. https://doi.org/10.1002/jmv.25871 PMID: 32281668

31. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. 2020; 92(4):441–47. https://doi.org/10.1002/jmv.25689 PMID: 31994742

32. Covid CDC, & Team, R. Severe outcomes among patients with coronavirus disease 2019 (COVID-19). MMWR Morb Mortal Wkly Rep 2020; 69(12), 343–346. https://doi.org/10.15585/mmwr.mm6912e2 PMID: 32214079

33. Kandil E, Attia AS, Youssef MR, et al. African Americans Struggle With the Current COVID-19. 2020; 272(3):e187–e90. https://doi.org/10.1097/sla.0000000000004185 PMID: 33759842

34. Price-Haywood EG, Burton J, Fort D, et al. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. 2020; 382(26):2534–43. https://doi.org/10.1056/NEJMsa2011686 PMID: 32459916

35. Prevention CfDCa. Adult Obesity Prevalence Maps 2019 [Available from: https://www.cdc.gov/obesity/data/prevalence-maps.html accessed March 18th 2021].

36. Han JH, Wilber ST. Altered mental status in older patients in the emergency department. Clinics in geriatric medicine 2013; 29(1):101–36. https://doi.org/10.1016/j.cger.2012.09.005 [published Online First: 2012/11/28]. PMID: 23177603