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Clinical Variables Associated With Impaired Consciousness in Hospitalized COVID-19 Patients

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Abstract

Background: **Impaired consciousness is associated with complications and mortality in COVID-19 patients. We study factors associated with impaired consciousness as measured by the Glasgow Coma Scale (GCS) in COVID-19 patients.**

Methods: **This is a retrospective study of 604 patients with COVID-19 in the metropolitan New York City area. We study the association of demographics, comorbidity, disease severity, treatment management, and laboratory measurements with both GCS nadir during hospitalization and GCS at discharge.**

Results: **Age was significantly associated with severe GCS nadir during hospitalization and at hospital discharge. Body mass index comorbidity was significantly associated with severe GCS at hospital discharge. Sedation treatment was significantly associated with both moderate and severe GCS nadir during hospitalization. Glucose nadir was significantly associated with severe GCS nadir during hospitalization. Sodium level at admission was associated with decreased relative risk while BUN peak level during hospitalization was associated with increased relative risk for severe GCS on discharge.**

Conclusion: **We found that factors from demographics, comorbidity, treatment management, and laboratory measurements were associated with GCS while disease severity was not significantly associated with GCS. These findings can guide clinicians for treatment approaches for the early identification of impaired consciousness and its degrees of severity in COVID-19 patients.**

Keywords: Covid-19, Altered level of consciousness, Glasgow coma scale, Sedatives, Neurological manifestations

1. Introduction

Neurologic manifestations are reported in as many as 80% of COVID-19 hospitalized patients[1,2] with over 30% reporting impaired consciousness.[1,3] Other neurologic manifestations of COVID-19 range from mild symptoms such as headache, dizziness, and anosmia, to severe complications including encephalopathy, stroke, motor, or sensory deficits.[2,4,5] There are differing hypotheses for the underlying mechanism for impaired consciousness, which include neurologic damage secondary to system dysfunction, hyper-immune response, and direct viral invasion.[4,6,7]

Among COVID-19 patients, impaired consciousness is a manifestation of those with severe disease and hypoxia.[8–10] However, there is limited research on the association of standard laboratory data among COVID-19 patients using the Glasgow Coma Scale (GCS) as a measure of impaired consciousness.[11,12] To our knowledge, only one prospective study showed a positive association between the extent of neuroradiological findings and markers of impaired consciousness as measured by the GCS in COVID-19 patients.[11] We are unaware of research that concurrently studies factors of demographics, comorbidity, disease severity, treatment management, and laboratory measurements with impaired consciousness as measured by the GCS in COVID-19 patients.

The primary goal of this study is to use the GCS[13] to objectively assess impaired consciousness of COVID-19 hospitalized patients. Furthermore, the study will examine the association of demographics,

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comorbidity, disease severity, treatment management, and laboratory measurements with both GCS nadir during hospitalization and GCS at discharge. This can potentially guide clinicians for the most relevant factors to focus upon during treatment of COVID-19 patients with impaired consciousness.

2. Methods

2.1. Setting and participants

This was a single-center retrospective study at a tertiary-care public hospital located in the New York Metropolitan area. Inclusion criteria were consecutive patients 1) age ≥18, 2) hospitalized, and 3) with a positive real-time-PCR-confirmed COVID-19 in nasopharyngeal samples from March 1, 2020 through May 15, 2020. All patients with 1) history of dementia, and 2) history of GCS less than 15 were excluded. A total of 604 consecutive patients were identified. All patients completed their hospital course and at study end were either discharged alive or deceased. The study was approved by the hospital Institutional Review Board. A waiver for informed consent was not needed due to the retrospective nature of the study.

2.2. Variables

Demographics were age, sex, and race/ethnicity [white, African American, Hispanic, or other]. Comorbidities were body mass index (BMI), and the Charlson Comorbidity Index (CCI). CCI ranges from 0 to 37, and is calculated based on age, and patient's medical history of cardiovascular diseases, history of dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, kidney diseases, history of malignancy, and AIDS status. A CCI of 2 points predicts a 90% estimated 10-year survival.[14] Disease severity consisted of requirement of ICU level of care at any time of hospitalization (no/yes), and oxygen requirement during hospitalization [none, low fraction of inspired oxygen (FiO2) ≤55%, high FiO2 >55% or requirement of invasive mechanical ventilation]. Treatment management consisted of administration of steroids and administration of sedative medicine at any time during hospitalization (including propofol, benzodiazepine, and/or haloperidol). Laboratory measurements consisted of serum sodium level on admission (mmol/L), serum blood urea nitrogen (BUN) level on admission (mg/dL), peak BUN level during hospitalization (mg/dL), glucose nadir (mg/dL), glucose peak (mg/dL), and glucose level at discharge (mg/dL). GCS[13] was recorded on admission, at nadir during hospitalization, and at hospital discharge. GCS was classified into three categories of normal/mild impairment (GCS 13–15), moderate impairment (GCS 9–12), or severe impairment (GCS 3–8).[15] The outcomes were GCS nadir during hospitalization and GCS at discharge.

2.3. Statistical analysis

Mean and standard deviation were used to describe the continuous variables. Frequency and percentage were used to describe the categorical variables. Multinomial multivariate logistic regression was used to study the outcome variables. Stata SE Version 17 (College Station, TX) was used for the analyses. All p-values were two tailed. Alpha level for significance was $p < 0.05$.

3. Results

For demographics, the mean age was 57 years, more than one third were female, and almost half were Hispanic. For comorbidities, mean BMI was 30 and mean CCI was 2.4. For disease severity, more than one third required ICU level of care and 10.9% required mechanical ventilation. For treatment management, steroid and sedative medication use was low at 2% and 15.7% respectively. For laboratory measurements, mean serum level of sodium upon hospital admission was 138 mmol/L which is within normal range. Mean serum BUN upon admission of 22.7 mg/dL and at peak during hospital stay of 34.1 mg/dL were each mildly elevated. GCS scores for severe impairment were 1.3% at admission, 5.6% at nadir during hospitalization, and 4.8% on discharge (see Table 1).

Table 2 shows the multinomial multivariate logistic regression analysis for GCS nadir during hospitalization. In the analysis for moderate GCS impairment at nadir, sedation and moderate GCS impairment at admission were each significantly positively associated with increased relative risk. None of the demographics, comorbidities, disease severity, or laboratory measurements were significantly associated with moderate GCS impairment at nadir. In the analysis for severe GCS impairment at nadir, age and glucose on discharge were each significantly positively associated with slightly increased relative risk, sedation and moderate GCS impairment at admission were each significantly positively associated with increased relative risk, and glucose nadir was significantly negatively associated with decreased relative risk. Comorbidities and disease severity were not significantly associated with severe GCS impairment.

Table 1. Sample characteristics of 604 patients with COVID-19 evaluated with the glasgow coma scale.

Variables	M (SD) or Frequency (Percent)
Demographics	
Age (years) [mean]	57.3 (16.04)
Sex (female)	249 (41.2)
Race/ethnicity	
Caucasian	129 (21.4)
African American	138 (22.9)
Hispanic	301 (49.8)
Other	36 (6.0)
Comorbidities	
Body mass index (kg/m^2) [mean]	30.0 (7.14)
CCI [mean]	2.4 (2.21)
Disease severity	
ICU (yes)	226 (37.4)
Oxygen requirement hospitalization	
None	126 (20.9)
Low FiO2 (≤55%)	257 (42.6)
High FiO2 (>55%)	155 (25.7)
Mechanical ventilation	66 (10.9)
Treatment management	
Steroid (yes)	12 (2.0)
Sedation (yes)	95 (15.7)
Laboratory measurements	
Sodium level at admission [mean]	138.4 (4.67)
BUN level at admission [mean]	22.7 (24.84)
BUN peak level during hospitalization [mean]	34.1 (39.16)
Glucose nadir [mean]	100.3 (48.65)
Glucose peak [mean]	214.5 (135.11)
Glucose on discharge [mean]	141.7 (77.10)
Glasgow Coma Scale	
Glasgow Coma Scale at admission	
Mild (13–15)	575 (95.2)
Moderate (9–12)	21 (3.5)
Severe (3–8)	8 (1.3)
Glasgow Coma Scale nadir during hospitalization	
Mild (13–15)	538 (89.1)
Moderate (9–12)	32 (5.3)
Severe (3–8)	34 (5.6)
Glasgow Coma Scale on discharge/death/latest day	
Mild (13–15)	557 (97.2)
Moderate (9–12)	18 (3.0)
Severe (3–8)	29 (4.8)

Note: M = mean, SD = standard deviation, CCI=Charlson Comorbidity Index, ICU = intensive care unit, BUN = blood urea nitrogen.

Table 3 shows the multinomial multivariate logistic regression analysis for GCS on discharge. In the analysis for moderate GCS impairment, glucose on discharge was significantly positively associated with slightly increased relative risk and moderate GCS impairment at admission was significantly positively associated with increased relative risk. None of the demographics, comorbidities, disease severity, or treatment management variables were significantly associated with moderate GCS impairment. In the analysis for severe GCS impairment, age, BMI, and glucose on discharge were each positively significantly associated with slightly increased relative risk. BUN peak level during hospitalization, moderate GCS impairment at admission, and severe GCS impairment at admission were each significantly positively associated with increased relative risk. Sodium level at admission was significantly negatively associated with decreased relative risk. None of the disease severity or treatment management variables were significantly associated with severe GCS impairment.

4. Discussion

We found that a moderate GCS score at admission and sedation use during hospitalization were each significantly associated with increased relative risk of having moderate or severe GCS nadir scores during hospitalization. Also, for severe GCS nadir scores during hospitalization, age and glucose on discharge were each significantly positively associated with slightly increased relative risk while glucose nadir was significantly negatively associated with decreased relative risk. For GCS at discharge, we found that a moderate GCS score at admission was significantly associated with increased relative risk of having moderate or severe GCS at discharge. Glucose at discharge was significantly positively associated with a slightly increased relative risk of having moderate or severe GCS at discharge. Unlike by GCS nadir, sedation during hospitalization was not significantly associated with moderate or severe GCS at discharge. For severe GCS scores at discharge, age, BMI, and BUN peak levels during hospitalization were each significantly positively associated with increased relative risk at discharge while sodium level at admission was associated with decreased relative risk at discharge.

We found that sedation use was associated with increased relative risk for both moderate and severe GCS nadir during hospitalization while there was no association of sedation use with GCS at discharge. Other studies have shown that sedative polypharmacy of four or more sedatives used simultaneously was associated with the development of delirium in COVID-19 patients in the intensive care unit as measured by the positive Confusion Assessment Method for the ICU (CAM-ICU).[16] Our study of mostly non-intensive care unit COVID-19 patients with sedative polypharmacy had nadir GCS scores similar to this pattern. We suggest that the cognitive impairment from sedation use during hospitalization was associated with moderate and severe GCS nadir values during hospitalization due to the intrinsic impact of sedatives on consciousness level, which may have contributed to

Table 2. Multinomial logistic regression analysis for glasgow coma scale nadir during hospitalization.

Variable	Moderate vs. Mild (reference) RRR (95% CI)	p-value	Severe vs. Mild (reference) RRR (95% CI)	p-value
Demographics				
Age (years)	0.98 (0.93, 1.04)	0.50	1.09 (1.01, 1.16)	0.03
Sex (female)	1.34 (0.40, 4.53)	0.64	0.86 (0.22, 3.35)	0.82
Race/ethnicity				
Caucasian	1.00		1.00	
African American	1.03 (0.22, 4.83)	0.97	0.30 (0.05, 1.92)	0.20
Hispanic	1.20 (0.26, 5.53)	0.82	0.64 (0.13, 3.24)	0.59
Other	0.38 (0.04, 3.73)	0.41	0.47 (0.03, 6.61)	0.58
Comorbidities				
Body mass index (kg/m^2)	0.98 (0.90, 1.06)	0.60	1.07 (1.00, 1.16)	0.07
CCI [mean]	0.97 (0.67, 1.39)	0.85	0.91 (0.61, 1.37)	0.66
Disease severity				
ICU (yes)	6.03 (0.48, 76.29)	0.17	8.33 (0.06, 1132.93)	0.40
Oxygen requirement hospitalization				
None	1.00		1.00	
Low FiO2 (≤55%)	10.59 (0.14, 789.50)	0.28	1.65 (–, –)	1.00
High FiO2 (>55%)	4.81 (0.05, 500.41)	0.51	5,405,883 (–, –)	0.99
Mechanical ventilation	24.88 (0.23, 2645.57)	0.18	4,192,830 (–, –)	0.99
Treatment management				
Steroid (yes)	7.18*e^{-8} (–, –)	1.00	3.54*e^{-8} (–, –)	1.00
Sedation (yes)	5.65 (1.49, 21.33)	0.01	6.76 (1.60, 28.49)	0.01
Laboratory measurements				
Sodium level at admission	0.96 (0.88, 1.05)	0.37	0.92 (0.83, 1.02)	0.11
BUN level at admission	1.23 (0.10, 14.77)	0.87	0.06 (0.004, 1.19)	0.07
BUN peak level during hospitalization	4.00 (0.43, 37.01)	0.22	8.56 (0.70, 104.83)	0.09
Glucose nadir	0.83 (0.02, 42.68)	0.93	0.01 (0.00008, 0.54)	0.03
Glucose peak	0.997 (0.994, 1.00)	0.25	1.00 (0.997, 1.01)	0.69
Glucose on discharge	1.01 (0.999, 1.02)	0.08	1.01 (1.001, 1.02)	0.03
Glasgow Coma Scale				
Glasgow Coma Scale at admission				
Mild (13–15)	1.00		1.00	
Moderate (9–12)	1077.15 (119.42, 9715.35)	<0.001	231.48 (13.42, 3993.19)	<0.001
Severe (3–8)	0.01 (–, –)	1.00	3.21*e^{+18} (–, –)	1.00

Note: RRR = relative risk ratio, CI = confidence interval, CCI=Charlson Comorbidity Index, ICU = intensive care unit, BUN = blood urea nitrogen. BUN level at admission, BUN peak level during hospitalization, and glucose nadir are for logarithmic transformed values due to presence of skewness. Pseudo R square = 0.61.

worsening mental status level. In contrast, sedation use was not significantly associated with GCS as discharge. The sedation impact can diminish due to down-titration or discontinuation close to discharge.[17] This could explain the lack of association of sedation use with GCS at discharge.

Our study showed that increased age was associated with increased odds of severe GCS nadir during hospitalization. Older age is associated with increased altered mental status (AMS) (i.e., impaired consciousness).[18] AMS can be an initial manifestation of COVID-19 infection in older patients and can be associated with more severe disease.[3] Furthermore, there is a positive association between AMS on admission and worsened mental status with severe disease.[3,20] We suggest that the increased odds of severe GCS nadir in older patients might be due to presence of more severe disease, possibly as a consequence of the predisposition of this patient population to present with several etiologies that carry high risk for developing AMS, in the setting of severity.

Glucose nadir was significantly associated with decreased relative risk for severe GCS nadir during hospitalization. High glucose levels are associated with more severe disease in COVID-19 patients, which is associated with impaired mental status.[21] However, to our knowledge, there are no studies showing an association between normoglycemia and consciousness levels. As our mean values for glucose nadir were within normal limits, this suggests that normoglycemia may be a protective factor for severe impaired consciousness in COVID-19 patients.

We found that age and BMI were each positively associated with severe GCS score at discharge. Older age is independently associated with worsened mental status in COVID-19 patients.[18] This is consistent with our findings of the positive association of age with severe GCS at discharge. We are

Table 3. Multinomial logistic regression analysis for glasgow coma scale on discharge.

Variable	Moderate vs. Mild (reference) RRR (95% CI)	p-value	Severe vs. Mild (reference) RRR (95% CI)	p-value
Demographics				
Age (years)	1.05 (0.99, 1.12)	0.11	1.12 (1.04, 1.22)	0.003
Sex (female)	1.13 (0.29, 4.39)	0.86	1.08 (0.26, 4.40)	0.92
Race/ethnicity				
Caucasian	1.00		1.00	
African American	1.19 (0.24, 5.94)	0.84	0.41 (0.07, 2.51)	0.34
Hispanic	0.67 (0.26, 5.53)	0.68	0.67 (0.12, 3.79)	0.65
Other	0.68 (0.05, 8.71)	0.77	2.00 (0.17, 24.13)	0.59
Comorbidities				
Body mass index (kg/m^2)	0.94 (0.84, 1.06)	0.32	1.12 (1.03, 1.22)	0.01
CCI [mean]	0.91 (0.61, 1.34)	0.62	1.00 (0.67, 1.49)	0.66
Disease severity				
ICU (yes)	3.22 (0.22, 46.83)	0.39	4.50 (0.02, 1310.94)	0.60
Oxygen requirement hospitalization				
None	1.00		1.00	
Low FiO2 (≤55%)	6,746,110 (–, –)	1.00	0.09 (–, –)	1.00
High FiO2 (>55%)	5,359,412 (–, –)	1.00	4,516,964 (–, –)	0.99
Mechanical ventilation	6,959,107 (–, –)	1.00	2,129,442 (–, –)	0.99
Treatment management				
Steroid (yes)	2.72*e^{-8} (–, –)	1.00	4.14*e^{-8} (–, –)	1.00
Sedation (yes)	0.85 (0.14, 5.16)	0.86	4.27 (0.78, 23.35)	0.09
Laboratory measurements				
Sodium level at admission	0.93 (0.84, 1.02)	0.12	0.88 (0.79, 0.98)	0.02
BUN level at admission	0.40 (0.02, 8.79)	0.56	0.13 (0.01, 2.39)	0.17
BUN peak level during hospitalization	24.86 (0.96, 640.55)	0.053	17.78 (1.24, 255.78)	0.03
Glucose nadir	15.37 (0.27, 885.33)	0.19	0.10 (0.001, 7.38)	0.29
Glucose peak	1.00 (0.99, 1.003)	0.53	1.00 (0.997, 1.01)	0.55
Glucose on discharge	1.01 (1.0008, 1.02)	0.03	1.01 (1.003, 1.02)	0.01
Glasgow Coma Scale				
Glasgow Coma Scale at admission				
Mild (13–15)	1.00		1.00	
Moderate (9–12)	74.94 (9.12, 615.78)	<0.001	31.53 (2.20, 451.23)	0.01
Severe (3–8)	1.80*e^{-10} (–, –)	1.00	451.81 (14.36, 14,216.12)	0.001

Note: RRR = relative risk ratio, CI = confidence interval, CCI=Charlson Comorbidity Index, ICU = intensive care unit, BUN = blood urea nitrogen. BUN level at admission, BUN peak level during hospitalization, and glucose nadir are for logarithmic transformed values due to presence of skewness. Pseudo R square = 0.56.

not aware of any data regarding the association of BMI and neurological manifestations including decreased level of consciousness in COVID-19 patients. Our finding of a positive association of severe GCS at discharge with BMI can be explained by the known higher severity of disease in obese patients with COVID-19.[19] This high severity of disease is associated with impaired consciousness.[20] Another explanation could be linked to the high prevalence of obstructive sleep apnea in obese patients and intrinsic higher risk for hypoxia,[22] which is associated with severe GCS in COVID-19 patients.[12]

We found that BUN peak level during hospitalization was significantly associated with increased relative risk of severe GCS impairment at discharge. This finding is likely associated with the effects of uremia in the central nervous system which contributes to the development of toxic metabolic encephalopathy in COVID-19 patients.[23] We showed that increased sodium level at admission was significantly associated with decreased relative risk of severe GCS impairment at discharge. This finding may be due to the mean levels of sodium from our sample, which had values considered under the spectrum of normonatremia. Our study shows that higher sodium levels within the ranges of normonatremia on admission can be considered a protective parameter against severe GCS at the time of discharge.

We found that a moderate GCS score at admission was significantly associated with increased relative risk of having moderate or severe GCS at discharge. It is possible that a moderate level of impaired consciousness is present at the time of admission in COVID-19 patients that exhibit more severe symptoms at presentation, eventually progressing to a critical stage of the disease, which can result in worsening impaired consciousness. Consistent with this potential explanation of our finding, a study found that impaired consciousness was a common

symptom in the acute phase of COVID-19 infection, and that patients had moderate cognitive impairment at 9-month follow up.[24] Furthermore, the neurotropism of the virus leading to significant inflammation of the CNS in the critically-ill can be a cause of major impairment of consciousness in the acute phase of the disease,[25] which can progress as the disease worsens and lead to severe or even irreversible cognitive impairment.[26]

A strength of our study is that this is the first COVID-19 study to use the GCS to find an association between many characteristics of COVID-19 patients and impaired consciousness. Another strong point is that nearly half of our study population were Hispanic, which makes it unique and a point of reference for further studies within this demographic group in the U.S. This study has some limitations. First, the study was conducted in the initial phase of the pandemic and therefore the impact of COVID-19 vaccine implementation was not measured. Second, we only used GCS but did not include neurological imaging as an objective measure to correlate with the degree of impaired consciousness measured by the GCS. Third, this was a single center study.

In conclusion, we found that factors from demographics, comorbidity, treatment management, and laboratory measurements were associated with GCS while disease severity was not significantly associated with GCS. We recommend that clinicians prioritize the early identification of impaired consciousness and its degrees of severity in COVID-19 patients and treat possible reversible causes to avoid potentially irreversible complications.

Ethics information

The study was approved by the hospital Institutional Review Board.

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Conflict of interest

The authors have no conflict of interest.

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