Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19

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Abstract

**Objective:** The SARS-CoV2 virus is protean in its manifestations, affecting nearly every organ system. However, nervous system involvement and its impact on disease outcome are poorly characterized. The objective of the study is to determine if neurological syndromes are associated with increased risk of inpatient mortality.

**Methods:** 581 hospitalized patients with confirmed SARS-CoV2 infection, neurological involvement and brain-imaging were compared to hospitalized non-neurological COVID-19 patients. Four patterns of neurological manifestations were identified – acute stroke, new or recrudescent seizures, altered mentation with normal imaging, and neuro-COVID-19 complex. Factors present on admission were analyzed as potential predictors of in-hospital mortality, including sociodemographic variables, pre-existing comorbidities, vital-signs, laboratory values, and pattern of neurological manifestations. Significant predictors were incorporated into a disease-severity score. Patients with neurological manifestations were matched with patients of the same age and disease severity to assess the risk of death.

**Results:** 4711 patients with confirmed SARS-CoV2 infection were admitted to one medical system in New York City during a 6-week period. Of these, 581 (12%) had neurological issues of sufficient concern to warrant neuro-imaging. These patients were compared to 1743 non-neurological COVID-19 patients matched for age and disease-severity admitted during the same period. Patients with altered mentation (n=258, p =0.04, OR 1.39, CI 1.04 – 1.86) or radiologically confirmed stroke (n=55, p = 0.001, OR 3.1, CI 1.65-5.92) had a higher risk of mortality than age and severity-matched controls.

**Conclusions:** The incidence of altered mentation or stroke on admission predicts a modest but significantly higher risk of in-hospital mortality independent of disease severity. While other biomarker factors also predict mortality, measures to identify and treat such patients may be important in reducing overall mortality of COVID-19.
INTRODUCTION

Pulmonary symptoms are the most common in-hospital presentation of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Severely affected patients may have damage to the kidneys, liver or heart.\(^1\)\(^,\)\(^2\) Since the initial outbreak in Wuhan, China, neurological involvement has also been described: of 214 cases, 45% of hospitalized patients presented with headache or dizziness, while 5% of severely affected patients had a cerebrovascular accident.\(^1\) Other nervous system manifestations have been identified including anosmia, increased seizure frequency, recrudescence of stroke symptoms and Guillain-Barre syndrome.\(^3\)\(^-\)\(^8\) There are reports of large vessel occlusion in younger patients, necrotizing encephalitis, acute demyelinating encephalomyelitis, and meningoencephalitis, though these appear to be relatively rare.\(^9\)\(^-\)\(^12\) Clinical and pathological studies that have tested for the existence of the SARS-CoV-2 virus in the brain or cerebrospinal fluid have yielded variable results.\(^13\) It remains unclear whether acute neurologic manifestations impact mortality of SARS-CoV-2 illness and whether this risk is present in the absence of imaging findings.

The objective of this study was to evaluate factors present on admission - sociodemographic data, medical comorbidities, vital signs, laboratory assessments, and patterns neurological syndromes - as potential predictors of in-hospital mortality. We hypothesize that clinical evidence of diffuse brain impairment, independent of disease severity and in the absence of imaging findings, is associated with an increased risk of in-hospital mortality. The rationale behind this supposition is that a reduced level of arousal has been previously shown to increase mortality risk from other acute adult medical admission.\(^14\) Moreover, we suggest that the development of an acute stroke in the context of acute SARS-CoV-2 infection also incurs greater risk of mortality independent of age and disease severity. Stroke has been previously shown to be associated with an increased risk of mortality in other infectious disease processes.\(^15\)

METHODS

Standards, Protocols Approvals, Registrations and Patient Consents

This is a retrospective study of all patients admitted to 4 hospitals within a unified healthcare system in (BLINDED FOR REVIEW) between March 1\(^{st}\) and April 16\(^{th}\) 2020 with SARS-CoV-2. The study received approval from our institutional ethical standards committee.
on human experimentation. Written informed consent was waived by our institutional ethical standards committee given the retrospective design of the study. Information on demographics, comorbidities, admission laboratory values, admission medications, admission supplemental oxygen orders, discharge and mortality was identified through a healthcare surveillance software package (Clinical Looking Glass [CLG]; Streamline Health, Atlanta, Georgia) and review of the primary medical records.  

All patients with real-time reverse transcriptase–polymerase chain reaction (RT-PCR) positive assay testing for SARS-CoV-2 RNA were included. Patients not admitted or that died before admission were excluded, since they seldom had a full panel of laboratory studies, and full neurologic evaluation could not be assessed. For patients with multiple admission only the last reported was considered for analysis. Data was captured on May 7th, 2020, therefore follow up varied from 3 weeks to 80 days.

The neurological manifestations cohort consisted of patients exhibiting neurological conditions of sufficient severity to warrant a neurologically motivated radiographic imaging study - computed tomography (CT), magnetic resonance imaging (MRI), diagnostic cerebral angiography, or neurologic consultation. Patients without imaging were placed into the non-neurological cohort.

We reasoned that different neurological syndromes may have different prognoses and placed patients with acute stroke confirmed on imaging, new-onset seizures or recrudescent seizures in patients with epilepsy, and incidental brain lesions not related to SARS-CoV-2 illness into separate groups. Patients without imaging findings or neurophysiological abnormalities were divided into those with altered mentation (cognition or arousal), and those with normal mentation but well documented neurological signs and symptoms compatible with COVID-19, defined as headache, anosmia, ageusia, chemesthesis, vertigo, pre-syncope, paresthesias, cranial nerve abnormalities, ataxia, dysautonomia, skeletal muscle injury.

The stroke cohort was defined as patients with CT angiography or cerebral angiography confirming blockage of an intracranial vessel, or CT/MRI findings consistent with acute or subacute infarcts, intracerebral hemorrhage, or subarachnoid hemorrhage. The seizure cohort was based on a careful review of the record by senior epilepsy neurologists, who confirmed the presence of overt seizures or status epilepticus, and the presence or absence of a history of epilepsy. Anatomic brain lesions not related to SARS-CoV-2 illness were defined as the presence
of subdural hematoma, brain tumor, chronic infarction or non-specific non-vascular territory lesions in the cortex or white matter. All imaging findings were established through a review by two independent neuroradiologists.

The presence of altered mentation was determined through a review of the notes documenting the history and physical-examination generated by emergency room physicians, admitting physicians, or members of the neurology or neurosurgery service when a consultation was requested. Patients were placed into the altered mentation cohort if there was evidence for impaired cognition (defined as disorientation, confusion, agitation, or delirium), or for impaired arousal (defined as drowsiness, somnolence, lethargy, or obtundation). The neuro-COVID-19 complex was defined as normal orientation and arousal with signs and symptoms commonly associated with COVID-19 (including headache, anosmia, ageusia, chemesthesis, vertigo, pre-syncope, paresthesias, cranial nerve abnormalities, ataxia, dysautonomia, skeletal muscle injury).

In-hospital deaths and deaths in the National Death Registry was used to collect mortality. Only laboratory values obtained on admission were included. The comorbidities chosen were those used in the Charlson Comorbidity Index using the International Coding Disease coding system (ICD-10). Every patient’s medical record was queried for diagnoses occurring within 5 years of their index admission.

**Statistical analysis**

All analyses were conducted in IBM SPSS (v26.0, Armonk, NY: IBM Corp). For statistical analysis, we represented continuous measurements as means (and standard deviations) or as medians (and interquartile ranges) and categorical variables were expressed as numbers (and percentages). Comparisons between non-neurological and neurological groups were performed via two-sided t-tests, Wilcoxon rank-sum tests, or chi-square testing as appropriate. No data imputation was made for missing values.

Our primary outcome measure was in-hospital mortality. We first performed univariate analysis on potentially predictive candidates. Factors that were significant on initial univariate analysis were then evaluated for independence using multivariate logistic regression.

Our primary analysis utilized a 1:3 matched-control design. For each of the 581 patients with neurological manifestations patients, a computer algorithm performed a random search of the remaining 4130 patients to identify three patients having the same age and a 2019 novel
coronavirus disease (COVID-19) severity score but no neurological manifestations, and generating a matched-control cohort of 1743 patients. We then compared the neurological manifestations cohort to the matched controls. Since each patient had matching controls, subsets of patients within the neurological manifestations cohort were compared to their respective subsets of controls, thereby maintaining a match in age and severity score. We defined statistical significance as a p-value less than 0.05.

In a second analysis we used factors found to be independent predictors of in-hospital mortality in the multivariate analysis, to estimate hazard ratios (HRs) for death using a Cox proportional hazards model.\textsuperscript{18} The number of days from admission to in-hospital death was used as the time-to-event data. Patients that were discharged from the hospital was right-censored. We included 15 independent variables that we considered potentially relevant to in-hospital mortality.

Data Availability

Data not published within the article is available in a public repository and includes digital object identifiers. The anonymized data set is available at the website, Dryad at https://doi.org/10.5061/dryad.7d7wm37sz. Further anonymized data can be shared by request from any qualified investigator.

RESULTS

During a six-week period between March 1\textsuperscript{st} and April 16\textsuperscript{th}, 2020, a total of 4,711 patients with SARS-CoV-2 infection were hospitalized at the (BLINDED FOR REVIEW). Among these, 581 (12\%) individuals had neurological manifestations and neuro-imaging studies. These patients constituted the neurological manifestations cohort and included those with altered mentation n=258 (44\% of neurological group and 5.5\% of total SARS-CoV-2 group), normal mentation with other neurological signs and symptoms compatible with COVID-19 (neuro-COVID 19 complex) n=216 (37\% of neurological group and 4.6\% of total SARS-CoV-2 group), stroke n=55 (9\% of neurological group and 1.2\% of total SARS-CoV-2 group), seizures n=26 (4\% of neurological group and 0.7\% of total SARS-CoV-2 group), and other brain lesions n=26 (4\% of neurological group and 0.6\% of total SARS-CoV-2 group).
Out of the 258 patients in the altered mentation group, 61 (23.6%) had no clear toxic, metabolic disturbances or history of dementia or other premorbid cognitive disturbances. Whereas out of the 55 stroke cases, 36 corresponded to large vessel occlusions, 8 (22.2%) received intravenous thrombolysis, 12 (33.3%) underwent endovascular thrombectomy and 3 exhibited hemorrhagic transformation. Furthermore, 31 (56.4%) patients of the stroke cohort did not have any underlying comorbidities.

**Predictors of Mortality**

We applied univariate analysis across the entire cohort to assess the potential associations with in-hospital mortality of socio-demographics, comorbidities, vital-signs, laboratory values, and CNS manifestations (Table 1). Among the potential predictors of mortality were male gender, a history of chronic obstructive pulmonary disease, diabetes mellitus, or renal disease, older age, hypoxia, fever or hypotension, and abnormalities of laboratory values reflecting impairment of the lungs, liver, kidneys, coagulation cascades, and the immune system.\(^\text{16}\)

All variables with a p<0.100 on the univariate categorical analysis were included in a multivariate logistic regression which demonstrated that on admission, hypotension, advanced age, elevated serum levels of creatinine, C-reactive protein (CRP), hypoxia, reduced troponin, platelet count, increased aspartate aminotransferase (AST), deranged sodium, reduced lymphocyte count, high body metabolic index (BMI), and male gender are significant independent predictors for an increased risk of in-hospital mortality. (Table 2).\(^\text{19}\) Findings consistent with acute stroke (p <0.001, OR 3.49, CI [2.9-4.1]), and altered mentation (p=0.002, OR 1.61 CI [1.3-1.9]), were significant predictors for an increased risk of in-hospital mortality, independent of the other factors (Table 2).

**Predictors of Neurological Manifestations**

We also compared the incidence of the various parameters as potential correlates of neurological manifestations. There was a significant association between altered mentation and increasing age, Black race, Latino ethnicity, prior history of stroke, chronic obstructive pulmonary disease, congestive heart failure, and renal disease. Other significant correlates were mean arterial pressure <70 mmHg, D-dimer >3 mg/liter, platelets <150,000 per mm\(^3\), international normalized ratio (INR) >1.2, BUN >30 mg/dL, creatinine >1.5 µmol/liter, Procalcitonin >0.1 ng/ml, and Troponin >0.1 ng/ml (Table 3). Patients with stroke had similar
characteristics to the larger non-neurologic cohort except for a significant higher percentage of patients with D-dimer levels >3mg/liter (55% versus 30%, p=0.001, 95% CI [1.6-5.0], Table 4). Patients in the seizure group were significantly younger than those in the non-neuro group (57 years versus 63 years, p=0.029, 95% CI [-11.9 --0.63]), and had significantly higher levels of IL-6 (5145 pp vs 262, p < 0.001, Table e-1). Table e-1 is available from Dryad: https://doi.org/10.5061/dryad.7d7wm37sz.

**Disease severity score**

In order to test the hypothesis that altered mentation or stroke carry an additional risk of in-hospital mortality, we sought to account for underlying disease severity in the most straightforward fashion possible. On univariate analysis, twenty-four factors had a significant association with mortality (Table 1), while multivariate regression demonstrated that fourteen of these were independent predictors of in-hospital mortality on admission – increasing age, hypotension, hypoxemia, elevated serum levels creatinine, CRP, D-dimer, and relative thrombocytopenia (Table 2).

Based on the respective odds rations of these variables, we created a scoring system reflecting underlying disease severity. Our goal was to capture the impairment in multiple organ-systems, without over-fitting the data. The score included: 1. age by decile, so that patients above 60, 70, or 80 received one, two or three points respectively; 2. hypotension, so that calculated mean arterial pressure (MAP) below 80, 70, and 60 received one, two, or three points respectively; 3. impaired pulmonary function, reflected in oxygen saturations below 94%, received one point; 4. impaired renal function, reflected in blood urea nitrogen greater than 30, received one point; 5. coagulopathy, reflected as an INR greater than 1.2 and increased inflammatory response, reflected in CRP levels greater than 10, received one point. The maximum score was 10 points (Table e-2). Table e-2 is available from Dryad: https://doi.org/10.5061/dryad.7d7wm37sz.

This scoring system was applied to the entire cohort, and the majority of patients were distributed in the first 3 points of the score and, moreover, the severity score corresponded to a linear increase for in-hospital mortality over the range of 0-10 points (Figure 1).

**Matched case-control analysis**
For each of the 581 patients with neurological manifestations, a random search algorithm identified three age and severity matched patients, generating a cohort of 1180 controls. Since age and severity score were deliberately matched, the distribution of age and disease severity was the same in the CNS groups and the matched-control group. Other variables were not explicitly matched, and exhibited small differences (Table 5).

Within the neurological manifestation groups, patients with stroke had the highest risk of in-hospital mortality, which was significantly higher than matched controls (49% versus 24%, p=0.001, OR 3.1, 95% CI [1.65-5.92]. The same was true for patients with altered mentation but the absence of imaging abnormalities (40% versus 33% respectively, p =0.04, OR 1.39 [1.04-1.86]). There was a trend for patients presenting with impaired arousal to have a higher risk of mortality compared to those with impaired cognition, although this was not statistically significant. There was no significant increase in risk for patients with new or recurrent seizures, neuro-COVID-19 complex, or those with incidentally discovered brain lesions (Table 5).

**Cox Proportional Hazards Model**

From the original set of 40 potential predictors of mortality, univariate analysis identified 24 that exhibited a significant correlation, and multivariate regression identified 14 as independent predictors of mortality. They also appear to combine in a broadly additive manner as demonstrated in the severity score and matched-control analysis. These considerations informed the choice of predictor variables in a Cox Proportional Hazards Model. We included advanced age, male gender, and elevated BMI as all have been previously associated with poor clinical outcomes. We included blood pressure on admission, as it had the largest odds ratio on multi-variate analysis. We included platelets, given the potential role of coagulopathy in stroke, creatinine to capture kidney damage, AST to capture liver damage, CRP to capture inflammatory derangement, troponin to capture cardiac injury, along with lymphocyte count to capture immune-system dysfunction. We also included stroke, altered mentation, and neuro-COVID-19 complex as potential predictors. Time-to-event data was the time from admission to in-hospital death. Patients discharged from the hospital were right-censored.

Multiple factors were found were independently associated with in-hospital mortality: hypotension (p < 0.0001, HR 4.39, CI 4.2-4.5), older age (p < 0.001, HR 2.61, CI 2.5-2.7), hypoxia (p < 0.001, HR 1.43, CI 1.3-1.5), elevated creatinine (p<0.001, HR 1.5, CI 1.4-1.6), elevated C-reactive protein (p<0.001, HR 1.42 CI [1.3-1.6]), lymphocytopenia (p < 0.00, HR
1.37, CI 1.2-1.5), elevated troponin (p=0.001, HR 1.34 CI 1.2-1.5) hypo- or hyper-
natremia(p=0.01, HR 1.23, CI 1.1-1.4), thrombocytopenia (p=0.003, HR 1.23 CI 1.1-1.4) and
elevated AST (p=0.01, HR 1.17 CI 1.0-1.3) (Table 6). Altered mentation was a significant
independent predictor of in-hospital mortality (p < 0.003, HR 1.37 CI 1.2-1.6), with the hazard
ratio suggesting that the risk is similar to that imposed by cardiac injury. Stroke is also a
significant predictor of mortality (p=0.004, HR 1.75 CI 1.4-2.1), with the hazard ratio between
hypoxia and age greater than 65.

**Discussion**

We present the largest inpatient cohort of SARS-CoV-2 infected patients to date, in
evaluating predictors of inpatient mortality as they relate to neurologic syndromes at
presentation. The neurologic findings seen in this cohort were similar to other large cohort
studies. A small but substantial subset of patients had associated neurological presentations
of sufficient severity to warrant imaging of the neuraxis. Although the majority had normal
neuro-imaging, the distinction between those with altered cognition or arousal and those
exhibiting other neurological signs and symptoms associated with COVID-19 infection (neuro-
COVID-19 complex) appears to be important. The etiology of altered mentation in COVID-19 is not clear. In this study there was an
association between altered mentation and hypotension, renal impairment as demonstrated by
elevated BUN and creatinine, disturbed coagulation as evidenced by elevated D-dimer levels,
prolonged INR and reduced platelet counts, and increased inflammation as evidenced by
elevated levels of procalcitonin. These biomarker abnormalities are associated with multi-organ
system failure and more severe SARS-CoV-2 illness. These patients were less likely to have
traditional symptoms such as fever or decreased oxygen saturation. It is unclear whether these
findings are exclusive to COVID-19 infection. Other studies have shown that delirium is a
predictor for increased inpatient mortality irrespective of underlying diagnosis, particularly in
elderly patients. Even when controlling for biomarker abnormalities, patients with impaired
cognition or arousal without abnormal neuro-imaging findings exhibited an increased risk of
inpatient mortality – suggesting that other yet-to-be determined mechanisms may be at play.
Irrespective of the etiological factors, such neurological presentations can be subtle but important
indications of more severe SARS-CoV-2 illness and should be taken seriously in hospital
emergency rooms. While other biomarker findings such as hypotension, D-dimer, coagulopathy,
and renal failure may be more predictive of illness severity, and mortality, neurologic syndromes in of itself still portends a higher risk of mortality, and can be easily assessed early on in a patient encounter. The biomarkers we found to be most correlative with poor outcome and potentially modifiable such as BUN, INR, oxygen saturation, mean arterial pressure and CRP could serve as potential targets for future research for treatments and or management paradigms.  

Stroke with concomitant SARS-CoV-2 infection is a rare but serious complication of the illness. In our cohort stroke represented 9% of our neurological cohort and 1% of all SARS-CoV-2 patients. This subgroup was more likely to have elevated D-dimer and CRP compared with controls. Stroke with SARS-CoV-2 infection had an even higher risk of inpatient mortality and these individuals likely represent a more severe manifestation of the illness. The etiology of stroke and SARS-CoV-2 infection is likely multifactorial, with some that can be attributed to the unique COVID-19 coagulopathy, severe systemic inflammatory reactions, and patients with risk factors for stroke in which the illness can a trigger. We discovered that more than half of the stroke patients did not have underlying risk factors, which is highly unusual. This does suggest like in other studies that the SARS-CoV-2 infection is itself a risk factor for stroke. During the time period of the study, all acute stroke patients were managed according to our institutional protocols and policies. Despite other changes to hospital throughput the neurologic services remained stable. An important caveat to note is that all patients that carry the diagnosis of acute ischemic stroke carry an increased risk of mortality compared to those without stroke on admission. The mortality risk therefore may be intrinsically predicated with the stroke diagnosis as compared to the SARS-CoV-2 infection itself.

Due to the retrospective nature of this study, there are potential limitations to this study. The majority of patients were a minority urban population and occurring at an epoch during a major surge period of the pandemic. This may bias the results toward higher mortality, as this was a great strain on treating hospitals at the time. This study was limited to evaluating inpatient mortality therefore any deaths that occurred outside of our healthcare system may have been lost. The health system during this epoch was over total capacity for critical care beds however not over capacity for beds, which may have limited the number of patients receiving neurologic consultation, adequate neurologic examination documentation, and neurologic imaging. It is also possible that minor stroke cases could have easily been missed in severe SARS-CoV-2 illness. Therefore, this may underestimate the true number of patients with neurologic manifestations.
found in our cohort. Despite this however using a matched analysis, neurologic symptoms alone still did predict higher inpatient mortality. We therefore hypothesize that in a prospective study, during non-pandemic volumes, the predictive effect of neurologic manifestations on mortality may be greater than perceived in this study.

Unlike other studies, in our institution we did not find significant differences in mortality in our Black and Latinx populations, when controlling for underlying comorbid illness.\textsuperscript{25-27} This further suggests that variations in outcome based on race and ethnicity are less tied to bias within the healthcare-related bias, and more likely a result of structural and systemic racism, leading to inequity of health as it pertains to comorbid conditions, and overall health of populations.\textsuperscript{28} We believe these findings correspond in the neurologic realm as it does with the SARS-CoV-2 infection itself.

To our knowledge, this is the largest study analyzing the neurological manifestations of Covid-19 and their effect on mortality. Documented CNS manifestations such as encephalopathy, stroke, seizure, and syncope are relatively common, being present in at least 13\% of hospitalized Covid-19 patients, though the incidence is likely much higher. Within the spectrum of CNS manifestations, altered mentation and stroke confer a higher risk of mortality above and beyond the severity of underlying illness. The presence of these syndromes may represent a different clinically important syndromic expression of SARS-Cov-2 infection which carries a greater risk of mortality and may benefit from targeted treatment.
Table 1. Univariate analysis of predictors for mortality in COVID-19 patients.

| VARIABLES                                   | Deceased (n=1148) | Survived (n=3563) | P value |
|----------------------------------------------|-------------------|-------------------|---------|
| **Categorical, n (%)**                       |                   |                   |         |
| Male                                         | 674 (58.7)        | 1837 (51.6)       | <0.001  |
| Black                                        | 408 (35.5)        | 1335 (37.5)       | 0.25    |
| White                                        | 134 (11.7)        | 332 (9.3)         | 0.02    |
| Asian                                        | 38 (3.3)          | 83 (2.3)          | 0.09    |
| Latino                                       | 405 (35.3)        | 1348 (37.8)       | 0.12    |
| Myocardial Infarction (MI)                   | 477 (41.5)        | 249 (6.9)         | <0.001  |
| Peripheral Vascular Disease (PVD)            | 135 (11.8)        | 678 (19)          | <0.001  |
| Congestive Heart Failure (CHF)               | 150 (13.1)        | 391 (11)          | 0.08    |
| Cerebrovascular Disease (CVD)                | 133 (11.6)        | 373 (10.5)        | 0.35    |
| Dementia                                     | 103 (9)           | 269 (7.5)         | 0.19    |
| Chronic Obstructive Pulmonary Disease (COPD) | 80 (7)            | 185 (5.2)         | 0.05    |
| Diabetes Mellitus Complicated                | 115 (10)          | 380 (10.7)        | 0.58    |
| Diabetes Mellitus Simple                     | 167 (14.5)        | 516 (14.5)        | 0.96    |
| Renal Disease                                | 235 (20.5)        | 598 (16.8)        | 0.01    |
| **Continuous**                               |                   |                   |         |
| Mean age (SD)-years                          | 72.0 (13.2)       | 60.6 (16.8)       | <0.001  |
| Mean Body Mass Index (SD)-kg/m²              | 26.2 (12.0)       | 28.0 (11.4)       | 0.01    |
| Median Oxygen saturation (IQR)-%             | 93 (85-97)        | 95 (92-98)        | <0.001  |
| Median Temperature (IQR)- °C                 | 37.1 (36.7-37.8)  | 37.1 (36.7-37.1)  | 0.01    |
| Median Systolic blood pressure (IQR)- mmHg  | 108 (85-133)      | 125 (112-154)     | <0.001  |
| Median Mean Arterial Pressure (MAP) (IQR)- mmHg | 76 (55-89.7)    | 89.7 (79.7-97)    | <0.001  |
| Median D-Dimer (IQR)- mg/liter               | 2.8 (0.27-5.6)    | 1.4 (0.3-2.6)     | <0.001  |
| Median Platelets (IQR)- k per mm³            | 198 (149-265.5)   | 219 (161-282)     | <0.001  |
|                                | Median (IQR)     | Median (IQR)     | <p>0.001</p> |
|--------------------------------|------------------|------------------|---------------|
| Median International normalized ratio (INR) (IQR) | 1.1 (1-1.3)      | 1.1 (1-1.2)      |               |
| Median Blood urea nitrogen (BUN) (IQR) - mg/dL     | 33 (11-55)       | 16 (9-28)        | <p>0.001</p> |
| Median Creatinine (IQR) - µmol/liter                | 150 (100-290)    | 100 (80-150)     | <p>0.001</p> |
| Median Sodium (IQR) - mmol/liter                    | 138 (134-142.5)  | 137 (134-140)    | <p>0.001</p> |
| Median Glucose (IQR) - mmol/liter                   | 7.4 (6.2-10.3)   | 8.6 (6.7-12.8)   | 0.31          |
| Median Aspartate amino transferase (AST) (IQR) - U/liter | 50 (29-78)      | 37 (23-58)       | <p>0.001</p> |
| Median Alanine amino transferase (ALT) (IQR) - U/liter | 28 (16-44)     | 26 (15-43)       | 0.73          |
| Median White blood cell count (WBC) (IQR) - per mm³ | 8100 (5800-11300)| 7200 (5300-9900) | <p>0.001</p> |
| Median Lymphocytes (IQR) - per mm³                  | 900 (600-1300)   | 1000 (700-1500)  | <p>0.001</p> |
| Median Interleukin-6 (IL-6) (IQR) - pg/ml          | 81.4 (36.8-183)  | 29.7 (12.8-63.2) | <p>0.001</p> |
| Median Ferritin (median, IQR) - µg/liter            | 1032 (205-1597)  | 648 (156-1060)   | <p>0.001</p> |
| Median C-Reactive Protein (CRP) (IQR) - mg/liter    | 15.4 (2.9-22.6)  | 7.1 (0.6-13.9)   | <p>0.001</p> |
| Median Procalcitonin (IQR) - ng/ml                  | 0.7 (0.2-3.2)    | 0.1 (0.1-0.5)    | <p>0.001</p> |
| Median Troponin (IQR) - ng/ml                       | 0.02 (0.01-0.07) | 0.01 (0.01-0.01) | <p>0.001</p> |

**Neurological Manifestations, n (%)**

|                          | 199 (17.3) | 382 (10.7) | <p>0.001</p> |
|--------------------------|------------|------------|---------------|
| All neurological manifestations |           |            |               |
| Altered mentation        | 104 (9.1)  | 154 (4.3)  | <p>0.001</p> |
| Stroke                   | 27 (2.4)   | 28 (0.8)   | <p>0.001</p> |
| Seizure                  | 5 (0.4)    | 21 (0.7)   | 1.00          |
| Neuro-COVID-19 complex   | 58 (5.1)   | 158 (4.4)  | 0.37          |
| Other Brain Anatomic Lesions | 5 (0.4)  | 21 (0.6)   | 0.65          |

**Missing data (n, %):** Congestive heart failure (94, 2%), Dementia (141, 3%), Chronic Obstructive Pulmonary Disease (141, 3%), Oxygen saturation (188, 4%), Temperature (141, 3%), Mean arterial pressure (235, 5%), D-dimer (989, 21%), Platelets (141, 3%), INR (423, 9%), BUN (565, 12%), Creatinine (141, 3%), Sodium (188, 4%), Glucose (1366, 29%), AST (235, 5%), ALT (188, 4%), WBC (141, 3%), Lymphocytes (141, 3%), IL-6 (3109, 66%), Ferritin (1319, 28%), CRP (659, 14%), Procalcitonin (2072, 44%), and Troponin (659, 14%).
Table 2. Multivariate logistic regression analysis of in-hospital mortality predictors in COVID-19 patients.

| Predictors                                      | p value  | OR    | 95% CI   |
|------------------------------------------------|----------|-------|----------|
| Mean arterial pressure < 70 mmHg               | <0.001   | 17.57 | 17.2-17.9|
| Stroke                                          | <0.001   | 3.49  | 2.9-4.1  |
| Age greater than 65 years                       | <0.001   | 3.31  | 3.1-3.5  |
| Creatinine > 150 µmol/liter                     | <0.001   | 1.77  | 1.6-2.0  |
| C-reactive protein > 10 mg/liter                | <0.001   | 1.64  | 1.5-1.8  |
| Altered mentation                               | 0.002    | 1.61  | 1.3-1.9  |
| Oxygen saturation < 94%                         | <0.001   | 1.59  | 1.4-1.8  |
| Troponin < 0.1 ng/ml                            | 0.005    | 1.43  | 1.2-1.7  |
| Platelets < 150,000 per mm³                     | <0.001   | 1.43  | 1.2-1.6  |
| Aspartate aminotransferase >40 U/liter          | <0.001   | 1.41  | 1.2-1.6  |
| Hyponatremia or Hypernatremia                   | 0.023    | 1.30  | 1.1-1.5  |
| Lymphocyte count <1000 per mm³                  | 0.01     | 1.23  | 1.1-1.4  |
| BMI > 30 kg/m²                                  | 0.03     | 1.22  | 1.0-1.4  |
| Male Gender                                     | 0.04     | 1.18  | 1.0-1.3  |
| Renal disease                                   | 0.06     | 1.21  | 1.0-1.4  |
| Temperature > 38 °C                             | 0.06     | 1.21  | 1.0-1.4  |
| International Normalized Ratio > 1.2            | 0.10     | 1.18  | 1.0-1.4  |
| D-dimer > 3 mg/liter                            | 0.15     | 1.14  | 1.0-1.3  |
| Blood urea nitrogen >30 mg/dL                   | 0.43     | 1.09  | 0.9-1.3  |
| Neuro-COVID-19 complex                          | 0.85     | 1.04  | 0.7-1.4  |
| White Blood Cell Count >10.8 or <4.1 k per mm³  | 0.53     | 0.86  | 0.4-1.4  |
Table 3. Distribution of variables in COVID-19 positive patients with altered mentation.

| VARIABLE                        | Altered Mentation  | Non-neuro  | p value | OR (95% CI)       |
|---------------------------------|--------------------|------------|---------|-------------------|
|                                 | n=258              | n=4130     |         |                   |
| Male                            | 144 (56%)          | 2367 (53%) | 0.44    | 1.11 (0.9-1.4)    |
| Black                           | 119 (46%)          | 1624 (36%) | 0.002   | 1.49 (1.2-1.9)    |
| White                           | 29 (11%)           | 437 (10%)  | 0.45    | 1.16 (0.8-1.7)    |
| Asian                           | 8 (3%)             | 113 (3%)   | 0.54    | 1.23 (0.6-2.5)    |
| Latino                          | 75 (29%)           | 1678 (38%) | 0.01    | 0.68 (0.5-0.9)    |
| Myocardial Infarction (MI)      | 40 (16%)           | 686 (15%)  | 0.93    | 1.01 (0.7-1.4)    |
| PVD                             | 30 (12%)           | 783 (18%)  | 0.01    | 0.61 (0.4-0.9)    |
| Congestive Heart Failure (CHF)  | 42 (16%)           | 499 (11%)  | 0.02    | 1.51 (1.1-2.1)    |
| Cerebrovascular Disease (CVD)   | 38 (15%)           | 468 (11%)  | 0.05    | 1.45 (1.2-1.1)    |
| Dementia                        | 23 (9%)            | 349 (8%)   | 0.64    | 1.12 (0.7-1.7)    |
| COPD                            | 25 (10%)           | 240 (6%)   | 0.01    | 1.83 (1.2-2.8)    |
| DM Complicated                  | 29 (11%)           | 466 (10%)  | 0.68    | 1.08 (0.7-1.6)    |
| All Diabetes                    | 44 (17%)           | 639 (14%)  | 0.24    | 1.23 (0.9-1.7)    |
| Renal Disease                   | 62 (24%)           | 771 (17%)  | 0.01    | 1.51 (1.1-1.2)    |
| Age > 60 years                  | 220 (74%)          | 2765 (47%) | <0.001  | 3.53 (2.5-5.5)    |
| BMI > 30kg/m²                    | 227 (32%)          | 4065 (41%) | 0.07    | 0.70 (0.5-1)      |
| Oxygen Saturation < 94%         | 87 (36%)           | 1631 (38%) | 0.46    | 0.90 (0.7-1.2)    |
| Temperature > 38°C              | 31 (13%)           | 823 (19%)  | 0.01    | 0.62 (0.4-0.9)    |
| MAP < 70mmHg                     | 51 (21%)           | 532 (13%)  | <0.001  | 1.86 (1.4-2.6)    |
| D-Dimer > 3 µg/mL               | 81 (41%)           | 1070 (30%) | 0.003   | 1.58 (1.2-2.1)    |
| Platelets < 150 x10³/µL         | 55 (22%)           | 836 (19%)  | 0.28    | 1.19 (0.9-1.6)    |
| INR > 1.2                       | 70 (30%)           | 747 (18%)  | <0.001  | 1.89 (1.4-2.5)    |
| BUN > 30 mg/dL                  | 113 (53%)          | 1172 (30%) | <0.001  | 2.67 (2.3-5)      |
| Creatinine > 1.5 mg/dL          | 131 (53%)          | 1318 (30%) | <0.001  | 2.54 (2.3-3)      |
| Sodium < 139 or > 154 mEq/L     | 34 (14%)           | 558 (13%)  | 0.69    | 1.08 (0.7-1.6)    |
| Glucose <60 or > 500 mEq/L      | 10 (6%)            | 104 (3%)   | 0.13    | 1.76 (0.9-3.4)    |
| AST > 40 U/L                    | 120 (50%)          | 2001 (47%) | 0.47    | 1.11 (0.9-3.4)    |
| Test                    | Positive | Positive Rate | Negative | Negative Rate | p-Value | Confidence Interval |
|-------------------------|----------|---------------|----------|---------------|---------|---------------------|
| ALT > 40 U/L            | 55       | 22%           | 1237     | 29%           | 0.03    | 0.70 (0.5-1)        |
| WBC <4800 or > 10,800 /µL | 214      | 86%           | 3677     | 85%           | 0.65    | 1.10 (0.8-1.6)      |
| Lymphocytes < 1000 /µL  | 125      | 50%           | 1999     | 46%           | 0.22    | 1.18 (0.9-1.5)      |
| IL-6 > 150 pg/ml        | 20       | 17%           | 271      | 14%           | 0.42    | 1.23 (0.7-2)        |
| Ferritin > 300 ng/mL    | 140      | 79%           | 2421     | 75%           | 0.33    | 1.21 (0.8-1.7)      |
| C-Reactive Protein > 1 mg/dL | 90      | 43%           | 1763     | 47%           | 0.26    | 0.84 (0.6-1.1)      |
| Procalcitonin > 0.1 ng/ml | 109     | 71%           | 1615     | 55%           | <0.001  | 2.02 (1.4-2.9)      |
| Troponin > 0.1 ng/ml    | 46       | 20%           | 404      | 11%           | <0.001  | 2.08 (1.5-2.9)      |
Table 4. Distribution of variables in COVID-19 positive patients with Stroke.

| VARIABLE                      | Stroke n=58 | Non-neuro n= 4130 | p value  | OR (95% CI) |
|-------------------------------|-------------|-------------------|----------|-------------|
| Male                          | 27          | 2367              | 0.587    | 0.84 (0.5-1.4) |
| Black                         | 17          | 1624              | 0.400    | 0.76 (0.4-1.3) |
| White                         | 4           | 437               | 0.653    | 0.71 (0.3-2)  |
| Asian                         | 1           | 113               | 1.000    | 0.70 (0.1-5.1) |
| Latino                        | 20          | 1678              | 1.000    | 0.96 (0.6-1.7) |
| Myocardial Infarction (MI)    | 17          | 686               | 0.004    | 2.49 (1.4-4.4) |
| PVD                           | 3           | 783               | 0.018    | 0.27 (0.1-0.9) |
| Congestive Heart Failure (CHF)| 5           | 499               | 0.676    | 0.75 (0.3-1.9) |
| Cerebrovascular Disease (CVD) | 9           | 468               | 0.190    | 1.61 (0.8-3.3) |
| Dementia                      | 4           | 349               | 1.000    | 0.88 (0.3-2.5) |
| COPD                          | 5           | 240               | 0.249    | 1.64 (0.6-4.1) |
| DM Complicated                | 8           | 466               | 0.371    | 1.46 (0.7-3.1) |
| All Diabetes                  | 8           | 639               | 1.000    | 1.0 (0.5-2.1)  |
| Renal Disease                 | 12          | 771               | 0.476    | 1.30 (0.7-2.5) |
| Age > 60 years                | 50          | 4065              | 0.815    | 0.98 (0.4-2.5) |
| BMI > 30kg/m²                  | 37          | 2765              | 0.577    | 1.19 (0.7-2.1) |
| Oxygen Saturation < 94%       | 18          | 1631              | 0.670    | 0.84 (0.5-1.5) |
| Temperature > 38°C            | 8           | 823               | 0.598    | 0.75 (0.4-1.6) |
| MAP < 70mmHg                   | 10          | 532               | 0.214    | 1.57 (0.8-3.1) |
| D-Dimer > 3 µg/mL             | 26          | 1070              | 0.001    | 2.81 (1-6.5) |
| Platelets < 150 x10³/µL       | 9           | 836               | 0.730    | 0.83 (0.4-1.7) |
| INR > 1.2                     | 12          | 747               | 0.472    | 1.31 (0.7-2.5) |
| BUN > 30 mg/dL                | 14          | 1172              | 1.000    | 0.98 (0.5-1.8) |
| Creatinine > 1.5 mg/dL        | 15          | 1318              | 0.659    | 0.83 (0.5-1.5) |
| Sodium < 139 or > 154 mEq/L   | 6           | 558               | 1.000    | 0.87 (0.4-2) |
| Glucose <60 or > 500 mEq/L    | 2           | 104               | 0.375    | 1.58 (0.4-6.6) |
| AST > 40 U/L                  | 26          | 2001              | 0.473    | 1.26 (0.7-2.2) |
| Test                        | Value 1 | Percentage 1 | Value 2 | Percentage 2 | Value 3          | Value 4          |
|-----------------------------|---------|--------------|---------|--------------|------------------|------------------|
| ALT > 40 U/L                | 12      | 24%          | 1237    | 29%          | 0.533            | 0.77 (0.4-1.5)   |
| WBC <4800 or > 10,800 /µL  | 47      | 87%          | 3677    | 85%          | 0.848            | 1.21 (0.5-2.7)   |
| Lymphocytes < 1000 /µL     | 24      | 44%          | 1999    | 46%          | 0.891            | 0.93 (0.5-1.6)   |
| IL-6 > 150 pg/ml           | 2       | 13%          | 271     | 14%          | 1.000            | 0.87 (0.2-3.9)   |
| Ferritin > 300 ng/mL       | 33      | 80%          | 2421    | 75%          | 0.584            | 1.35 (0.6-2.9)   |
| C-Reactive Protein > 1 mg/dL| 25      | 54%          | 1763    | 47%          | 0.373            | 1.34 (0.8-2.4)   |
| Procalcitonin > 0.1 ng/ml  | 19      | 58%          | 1615    | 55%          | 0.862            | 1.07 (0.5-2.2)   |
| Troponin > 0.1 ng/ml       | 7       | 14%          | 404     | 10%          | 0.488            | 1.35 (0.6-3)     |
### Table 5. In-hospital mortality in patients with neurological manifestations and matched controls.

For each neurological patient there are three control patients matched for age and Covid-19 disease severity score.

| Neurological Manifestations | Neurological Cohort | Matched Controls | p value | OR (95%CI) |
|-----------------------------|---------------------|------------------|---------|------------|
| Admitted        | Deceased | Admitted | Deceased |         |
| All Neurological       | 581       | 199 (34%) | 1743     | 506 (29%) | 0.02 | 1.27 (1.04-1.56) |
| Altered Mentation    | 258       | 104 (40%) | 774      | 253 (33%) | 0.04 | 1.39 (1.04-1.86) |
| Stroke             | 55        | 27 (49%)  | 165      | 39 (24%)  | 0.001 | 3.1 (1.65-5.92) |
| Neuro-COVID-19 complex | 216     | 58 (27%)  | 648      | 173 (27%) | 0.85 | 1.0 (0.7-1.42) |
| Seizure             | 26        | 5 (19%)   | 78       | 13 (17%)  | 0.77 | 1.26 (0.4-3.98) |
| Incidental Brain Lesion | 26     | 5 (19%)   | 78       | 24 (30%)  | 0.36 | 0.54 (0.2-1.6) |
Table 6. Cox Regression Analysis for mortality outcomes

| Predictors                          | p value | HR  | CI    |
|-------------------------------------|---------|-----|-------|
| MAP < 70 mmHg                       | <0.001  | 4.39| 4.2-4.5|
| Age > 65 years                      | <0.001  | 2.61| 2.5-2.7|
| Stroke                             | 0.004   | 1.75| 1.4-2.1|
| Creatinine > 150 µmol/liter        | <0.001  | 1.50| 1.4-1.6|
| Oxygen Saturation < 94 %           | <0.001  | 1.43| 1.3-1.5|
| C Reactive Protein >10 mg/liter    | <0.001  | 1.42| 1.3-1.6|
| Lymphocyte count < 1000 per mm³    | <0.001  | 1.37| 1.2-1.5|
| Altered Mentation                  | 0.003   | 1.37| 1.2-1.6|
| Troponin > 0.1 ng/ml               | 0.001   | 1.34| 1.2-1.5|
| Hyponatremia or Hypernatremia      | 0.01    | 1.23| 1.1-1.4|
| Platelets < 150,000 per mm³        | 0.003   | 1.23| 1.1-1.4|
| AST > 40 U/liter                   | 0.01    | 1.17| 1.0-1.3|
| BMI > 30 kg/m²                     | 0.19    | 1.09| 1.0-1.2|
| Male Gender                        | 0.24    | 1.07| 1.0-1.2|
### Appendix 1

| Name                              | Location                  | Contribution                                                                 |
|-----------------------------------|---------------------------|------------------------------------------------------------------------------|
| Emad N Eskandar, MD               | Montefiore Medical Center | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |
| David J Altschul, MD              | Montefiore Medical Center | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |
| Rafael de La Garza Ramos, MD      | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content       |
| Phillip Cezayirli, MD             | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content       |
| Santiago R Unda, MD               | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content       |
| Joshua Benton, BA                 | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Joseph Dardick, BA                | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Aureliana Toma, MD                | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Nikunj Patel, BA                  | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Avinash Malaviya, BA, MS          | Montefiore Medical Center | Major Role in acquisition of data                                           |
| David Flomenbaum, BS              | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Jenelys Fernandez-Torres, BA      | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Jenny Lu, BA                      | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Ryan Holland, MD                  | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Elisabetta Burchi, MD             | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content       |
| Richard Zampolin, MD              | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Kevin Hsu, MD                     | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Andrew McClelland, MD             | Montefiore Medical Center | Major Role in acquisition of data                                           |
| Name                        | Institution            | Role in Data Contribution                          |
|-----------------------------|------------------------|---------------------------------------------------|
| Judah Burns, MD             | Montefiore Medical Center | Major Role in acquisition of data |
| Amichai Erdfarb, MD         | Montefiore Medical Center | Major Role in acquisition of data |
| Rishi Malhotra, MD          | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content |
| Michelle Gong, MD           | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content |
| Peter Semczuk, DDS, MPH     | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content |
| Victor Ferastraoaru, MD     | Montefiore Medical Center | Major Role in acquisition of data |
| Jillian Rosengard, MD       | Montefiore Medical Center | Major Role in acquisition of data |
| Daniel Antoniello, MD       | Montefiore Medical Center | Major Role in acquisition of data |
| Daniel Labovitz, MD         | Montefiore Medical Center | Interpreted the data; revised the manuscript for intellectual content |
| Charles Esenwa, MD          | Montefiore Medical Center | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |
| Mark Milstein, MD           | Montefiore Medical Center | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |
| Alexis Boro, MD             | Montefiore Medical Center | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |
| Mark F Mehler, MD           | Montefiore Medical Center | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |
REFERENCES

1. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 05 2020;97(5):829-838. doi:10.1016/j.kint.2020.03.005

2. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 05 2020;8(5):475-481. doi:10.1016/S2213-2600(20)30079-5

3. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: A literature review. *J Clin Neurosci*. May 2020;doi:10.1016/j.jocn.2020.05.017

4. 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*. Jul 2020;92(7):699-702. doi:10.1002/jmv.25915

5. Needham EJ, Chou SH, Coles AJ, Menon DK. Neurological Implications of COVID-19 Infections. *Neurocrit Care*. Apr 2020;doi:10.1007/s12028-020-00978-4

6. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. Apr 2020;doi:10.1001/jamaneurol.2020.1127

7. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. *J Neurol Sci*. Apr 2020;413:116832. doi:10.1016/j.jns.2020.116832

8. Jiménez-Ruiz A, García-Grimshaw M, Ruiz-Sandoval JL. Neurological manifestations of COVID-19. *Gac Med Mex*. May 2020;156(4)

9. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. Apr 2020;doi:10.1056/NEJMoa2009787

10. Al-Olama M, Rashid A, Garozzo D. COVID-19-associated meningoencephalitis complicated with intracranial hemorrhage: a case report. *Acta Neurochir (Wien)*. May 2020;doi:10.1007/s00701-020-04402-w

11. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. *Radiology*. Mar 2020:201187. doi:10.1148/radiol.202021187

12. Yaghi S, Ishida K, Torres J, et al. SARS2-CoV-2 and Stroke in a New York Healthcare System. *Stroke*. May 2020;STROKEAHA120030335. doi:10.1161/STROKEAHA.120.030335

13. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. *Cell*. Oct 2020;183(1):16-27.e1. doi:10.1016/j.cell.2020.08.028

14. Todd A, Blackley S, Burton JK, et al. Reduced level of arousal and increased mortality in adult acute medical admissions: a systematic review and meta-analysis. *BMC Geriatr*. Dec 2017;17(1):283. doi:10.1186/s12877-017-0661-7

15. Sasson G, Bai AD, Showler A, et al. Staphylococcus aureus bacteremia in immunosuppressed patients: a multicenter, retrospective cohort study. *Eur J Clin Microbiol Infect Dis*. Jul 2017;36(7):1231-1241. doi:10.1007/s10096-017-2914-y

16. Altschul DJ, Unda SR, Benton J, et al. A novel severity score to predict inpatient mortality in COVID-19 patients. *Sci Rep*. 10 2020;10(1):16726. doi:10.1038/s41598-020-73962-9

17. Altschul DJ, Unda SR, de La Garza Ramos R, et al. Hemorrhagic presentations of COVID-19: Risk factors for mortality. *Clin Neurol Neurosurg*. Jul 2020;198:106112. doi:10.1016/j.clineuro.2020.106112
18. Behman R, Nathens AB, Haas B, Look Hong N, Pechlivanoglou P, Karanicolas P. Surgery for adhesive small-bowel obstruction is associated with improved long-term survival mediated through recurrence prevention: A population-based, propensity-matched analysis. *J Trauma Acute Care Surg*. 09 2019;87(3):636-644. doi:10.1097/TA.0000000000002366

19. Matthiessen P, Hallböök O, Rutegård J, Sjödahl R. Population-based study of risk factors for postoperative death after anterior resection of the rectum. *Br J Surg*. Apr 2006;93(4):498-503. doi:10.1002/bjs.5282

20. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry*. 10 2020;7(10):875-882. doi:10.1016/S2215-0366(20)30287-X

21. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. Jul 2020;doi:10.1093/brain/awaa240

22. Silva TJ, Jerussalmy CS, Farfel JM, Curiati JA, Jacob-Filho W. Predictors of in-hospital mortality among older patients. *Clinics (Sao Paulo)*. 2009;64(7):613-8. doi:10.1590/S1807-59322009000700002

23. Nannoni S, de Groot R, Bell S, Markus HS. EXPRESS: Stroke in COVID-19: a systematic review and meta-analysis. *Int J Stroke*. Oct 2020;1747493020972922. doi:10.1177/1747493020972922

24. Amin R, Kitazawa T, Hatakeyama Y, et al. Trends in hospital standardized mortality ratios for stroke in Japan between 2012 and 2016: a retrospective observational study. *Int J Qual Health Care*. Nov 2019;31(9):G119-G125. doi:10.1093/intqhc/mzz091

25. Kabarriti R, Brodin NP, Maron MI, et al. Association of Race and Ethnicity With Comorbidities and Survival Among Patients With COVID-19 at an Urban Medical Center in New York. *JAMA Netw Open*. 09 2020;3(9):e2019795. doi:10.1001/jamanetworkopen.2020.19795

26. Gu T, Mack JA, Salvatore M, et al. COVID-19 outcomes, risk factors and associations by race: a comprehensive analysis using electronic health records data in Michigan Medicine. *medRxiv*. Jun 2020;doi:10.1101/2020.06.16.20133140

27. Bhargava A, Sharma M, Riederer K, Fukushima EA, Szpunar SM, Saravolatz L. Risk Factors for In-hospital Mortality from COVID-19 Infection among Black Patients - An Urban Center Experience. *Clin Infect Dis*. Sep 2020;doi:10.1093/cid/ciaa1468

28. Khazanchi R, Evans CT, Marcelin JR. Racism, Not Race, Drives Inequity Across the COVID-19 Continuum. *JAMA Netw Open*. 09 2020;3(9):e2019933. doi:10.1001/jamanetworkopen.2020.19933
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Editor’s Note: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

Dr. Frontera et al. examined the prevalence and associated mortality of well-defined neurologic diagnoses in a prospective, multicenter, observational study of 4,491 consecutive hospitalized adults in the New York City (NYC) metropolitan area with laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Neurologic disorders were diagnosed in 13.5% of these patients with coronavirus disease-2019 (COVID-19) and were associated with higher in-hospital mortality and lower likelihood of discharge home. In response, Dr. Kumar et al. contrast the most common neurologic clinical diagnoses in this study (toxic/metabolic encephalopathy, stroke, seizure, and hypoxic/ischemic brain injury) with the most common imaging diagnoses in another study by Dr. Kremer et al. of patients with COVID-19 who underwent brain MRI (ischemic strokes, leptomeningeal enhancement, and encephalitis). They note that the study by Dr. Frontera et al. reported raised protein in the CSF in several of the patients, suggestive of intrathecal inflammation as may be seen with meningitis/encephalitis, although white cell counts were low. They wonder whether the low frequency of brain MRI in the study may have led to underdetection of meningitis/encephalitis. In another response, Dr. Liotta et al. note that they reported similar rates of stroke, seizure, Guillain-Barre Syndrome, encephalitis, and meningitis in their recent Chicago-based study but had higher rates of encephalopathy. They note that in their own study, they adjudicated all charts, not just those for patients receiving neurologic consultations, and used protocolized delirium assessments to identify encephalopathy. They contend that Dr. Frontera et al. may have missed several cases of encephalopathy with their methodology and suggest that excluding headache as a neurologic symptom may have limited the scope of SARS-CoV-2 neuropathogenesis. They also note the lower in-hospital mortality in their cohort, potentially related to the absence of an overwhelming case surge in Chicago compared with NYC, and emphasize the importance of public health measures against COVID-19 to help sustain health care infrastructure. Responding to these comments, the authors question whether patients in the imaging study by Dr. Kremer et al. actually met accepted diagnostic criteria for encephalitis, noting that CSF SARS-CoV-2 RT-PCR (reverse transcription PCR) was negative in 20 patients and positing that some of the imaging findings could have represented postinfectious encephalitis. They also caution that many of the reported MRI findings are nonspecific and can be seen with nonencephalitic conditions, in particular hypoxic/ischemic injury, given the high frequency of acute respiratory distress syndrome and supplemental oxygen requirement among these patients. They also note that the elevated CSF protein in their own study is a nonspecific finding and highlight the need to follow rigorous standards when ascribing meningitis/encephalitis to SARS-CoV-2 infection. Regarding their lower rates of encephalopathy compared with the Chicago study, the authors argue that they coded toxic-metabolic encephalopathy only in patients off sedation or after a sedation washout, whereas the Chicago study may have included patients with sedation-related delirium, which may have different outcomes than other etiologies of encephalopathy. However, they acknowledge that they may have underestimated the overall prevalence of neurologic injury in the most critically ill patients who could not be assessed off sedation, or who were unable to express other neurologic symptoms. Notwithstanding the older age of their cohort, they agree that the critical surge and strain on health care resources in NYC likely affected mortality and echo the importance of public health measures to stem such surges. This exchange demonstrates important differences that can arise in incidence or frequency estimates of different neurologic manifestations in COVID-19 based on the methodology that is followed.

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Reader Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

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We read with interest the article by Frontera et al.\(^1\) studying neurologic disorders in hospitalized COVID-19 patients in New York City. The overall prevalence of neurologic disorders among hospitalized COVID-19 patients was 13.5%. The most common neurologic symptoms were toxic/metabolic encephalopathy (309/606, 51%), stroke (84/606, 14%), seizure (74/606, 12%), and hypoxic/ischemic brain injury (65/606, 11%). In a recent study by Kremer et al.,\(^2\) correlated neurologic and neuroimaging findings of COVID-19 patients concluded that among 64 patients with neurologic symptoms who underwent brain MRI, ischemic strokes (27%) were the most common finding, followed by leptomeningeal enhancement (17%) and encephalitis (13%).

Even in present study, the CSF findings (table 2) show raised protein [median 61, IQR (42–106) mg/dL], favoring intrathecal inflammation and possibility of meningitis and/or encephalitis. Although there were few cells in the CSF [2 (1–4)], in COVID-19 patients, atypical inflammatory response without CSF pleocytosis is not uncommon.\(^3\) Another possible explanation of not picking up any encephalitis or meningitis in the present study is the lesser number of brain MRI (15%) being performed. We are unable to understand the difference between stroke and hypoxic/ischemic brain injury because they were categorized separately in the current study!

1. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
2. Kremer S, Leroy F, Anheim M, et al. Neurologic and neuroimaging findings in patients with COVID-19. Neurology 2020;95:e1868–e1882.
3. Edén A, Kanberg N, Gustner J, et al. CSF biomarkers in patients with COVID-19 and neurological symptoms. Neurology 2020;96:e294–e300.

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Author Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

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We appreciate the comments by Kumar et al. on our article.\(^1\) The referenced Kremer study\(^2\) was a retrospective case series and included patients with positive MRI findings only. It is unclear whether the patients with the diagnosis of “encephalitis” met diagnostic or causal criteria outlined by the International Encephalitis Consortium\(^3\) and others.\(^4\) Indeed, CSF SARS-CoV-2 RT-PCR was negative in 20 patients. In 2 of 3 with CSF pleocytosis (>5 cell/mm\(^3\)), imaging was performed >2 weeks from symptom onset, possibly representing postinfectious autoimmune encephalitis and not infectious encephalitis. Many of the MRI findings described are nonspecific and can be seen in hypoxic/ischemic brain injury, metabolic encephalopathy, or postseizure. Notably, 100% of “encephalitis” patients required oxygen and 75% had ARDS, suggesting that a proportion of the MRI changes may represent hypoxic/ischemic injury (defined as a global insult due to hypoxemia, hypotension, or cardiac arrest). Although we detected elevated CSF protein in some patients,\(^1\) this is nonspecific and can be found in stroke, hemorrhage (or traumatic tap), hypoxic/ischemic injury, diabetes, uremia, tumor, neuropathy, and many other conditions. Because the implications of SARS-CoV-2 neurotropism are far reaching, we believe that it is critical to follow the most rigorous standards and criteria when ascribing encephalitis/meningitis/myelitis to SARS-CoV-2 infection.

1. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
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Reader Response: A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

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Frontera et al.¹ should be commended on the breadth of their report on neurologic diagnoses in COVID-19. Although stroke, seizure, GBS, encephalitis, and meningitis rates are similar to our recent study,² and others,³,⁴ their rates of encephalopathy were markedly lower (6.9% vs 31.8%).¹,² This likely reflects their methodology of adjudicating diagnoses only from chart review of patients with neurologic consultation. Our study similarly included patients with confirmed SARs-CoV-2 RT PCR and ascribed diagnoses by neurologist adjudication. We recognized that delirium—an entity within the encephalopathy spectrum—is the purview of multiple specialties.⁵ As such, encephalopathy would not reliably result in neurologic consultation; we adjudicated all charts and leveraged protocolized delirium assessments. The methodology of Frontera et al. likely failed to identify many encephalopathic patients, limiting their estimation of neurologic morbidity. Nevertheless, encephalopathy remained the most frequent neurologic diagnosis. In addition, prematurely excluding headache as a “neurologic symptom” limits the scope and understanding of SARS-CoV-2 neuropathogenesis. As we determine optimal management and decipher the long-term consequences of COVID-19 and encephalopathy, study methodologies should consider that not all neurologic complications result in in-hospital neurologic consultation. Consistently, neurologic manifestations of COVID-19 are common and encephalopathy impacts morbidity. Interestingly, despite similar ventilation rates (26.3% vs 22.0%), our cohort’s hospital mortality was considerably lower (8.4% vs 21.4%).¹,² Although New York experienced a critical strain on hospital infrastructure early in the pandemic, our Chicago area hospital system never experienced the same overwhelming case surge. Taken together, Frontera et al. and our study may reflect the magnitude of public health benefit that could be realized by avoiding case volumes that overwhelm health care infrastructure. This should further emphasize the benefit of universal masking, social distancing, and building redundancy into health care infrastructure.

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Author disclosures are available upon request (journal@neurology.org).
We appreciate these comments on our article. We coded toxic-metabolic encephalopathy only in patients off sedation or after an adequate sedation washout, in contrast to the Chicago study, which included patients who may have been receiving sedation or had a positive Confusion Assessment Method (CAM). Although sedation-related delirium has been associated with worse outcomes, the implications for long-term neurologic recovery differ based on the underlying etiologies of encephalopathy, which can best be ascertained when eliminating the confounding effect of sedative medications. Because a proportion of patients were too hypoxic for assessment off sedation, we recognize that we may be underestimating the overall prevalence of neurologic injury in the most critically ill patients. Similarly, hospitalized patients are often unable to express neurologic symptoms because of the severity of illness; hence, findings such as headache, anosmia, or dysgeusia are typically underrepresented and their prevalence is better studied in the outpatient setting. Although our cohort was somewhat older than the Chicago group—median age 65 vs 58 years—we agree that the critical surge and strain on resources in NYC likely impacted mortality rates, which were similarly high in other area hospitals during this time frame. Preventative efforts to stem such surges in hospitalizations—including masking and social distancing—are essential.

1. Frontera JA, Sabadia S, Lakhani R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York City. Neurology 2021;96:e575–e586.
2. Liotta EM, Butra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol 2020;7:2221–2230.
3. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763–1770.
4. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 2020;323:2052–2059.

CORRECTION

Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19

In the post-acceptance published version of the article “Neurologic Syndromes Predict Higher In-Hospital Mortality in COVID-19,” by Nader Eskandar et al., an author was accidentally omitted. The author byline and appendix should have included Jonathan Gursky, MD, from the Department of Neurology at Montefiore Medical Center, for his major role in acquisition of data. The omission is corrected in the final published version of the article. The authors regret the omission.

Reference

1. Nader Eskandar F, Altshuler DJ, de La Garza Ramos R, et al. Neurologic syndromes predict higher in-hospital mortality in COVID-19. Neurology Epub 2020 Dec 18.