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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 1st and April 16th 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.[16]

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) .[5,16]. 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).[17] 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.[16]

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.[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 1st and April 16th, 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 constitued 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.[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**).[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**).[16] 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 straight-forward 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.[16] 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.[6, 20, 21] 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 be 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.[22] 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.[16]

Stroke with concomitant SARS-CoV-2 infection is a rare but serious complication of the illness.[12] 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 be 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.[23] 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.[24] 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.[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.[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/m^2	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 mm^3	198 (149-265.5)	219 (161-282)	<0.001

Median International normalized ratio (INR) (IQR)	1.1 (1-1.3)	1.1 (1-1.2)	<0.001
Median Blood urea nitrogen (BUN) (IQR)- mg/dL	33 (11-55)	16 (9-28)	<0.001
Median Creatinine (IQR)- µmol/liter	150 (100-290)	100 (80-150)	<0.001
Median Sodium (IQR)- mmol/liter	138 (134-142.5)	137 (134-140)	<0.001
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)	<0.001
Median Alanine amino transferase (ALT) (IQR)- U/liter	28 (16-44)	26 (15-43)	0.73
Median White blood cell count (WBC) (IQR)- per mm^3	8100 (5800-11300)	7200 (5300-9900)	0.001
Median Lymphocytes (IQR)- per mm^3	900 (600-1300)	1000 (700-1500)	<0.001
Median Interleukin-6 (IL-6) (IQR)- pg/ml	81.4 (36.8-183)	29.7 (12.8-63.2)	<0.001
Median Ferritin (median, IQR)- µg/liter	1032 (205-1597)	648 (156-1060)	<0.001
Median C-Reactive Protein (CRP) (IQR)- mg/liter	15.4 (2.9-22.6)	7.1 (0.6-13.9)	<0.001
Median Procalcitonin (IQR)- ng/ml	0.7 (0.2-3.2)	0.1 (0.1-0.5)	<0.001
Median Troponin (IQR)- ng/ml	0.02 (0.01-0.07)	0.01 (0.01-0.01)	<0.001
Neurological Manifestations, n (%)			
All neurological manifestations	199 (17.3)	382 (10.7)	<0.001
Altered mentation	104 (9.1)	154 (4.3)	<0.001
Stroke	27 (2.4)	28 (0.8)	<0.001
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 mm^3	<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 mm^3	0.01	1.23	1.1-1.4
BMI > 30 kg/m^2	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 mm^3	0.53	0.86	0.4-1.4

Table 3. Distribution of variables in COVID-19 positive patients with altered mentation.

VARIABLE	Altered Mentation n=258		Non-neuro n= 4130		p value	OR (95%CI)
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)
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 (1·1-2)
Age > 60 years	220	74%	2765	47%	<0·001	3·53 (2·5-5)
BMI > 30kg/m^2	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 $_x10^3$/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)

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	49%	2367	53%	0·587	0·84 (0·5-1·4)
Black	17	31%	1624	36%	0·400	0·76 (0·4-1·3)
White	4	7%	437	10%	0·653	0·71 (0·3-2)
Asian	1	2%	113	3%	1·000	0·70 (0·1-5·1)
Latino	20	36%	1678	38%	1·000	0·96 (0·6-1·7)
Myocardial Infarction (MI)	17	31%	686	15%	0·004	2·49 (1·4-4·4)
PVD	3	5%	783	18%	0·018	0·27 (0·1-0·9)
Congestive Heart Failure (CHF)	5	9%	499	11%	0·676	0·75 (0·3-1·9)
Cerebrovascular Disease (CVD)	9	16%	468	10%	0·190	1·61 (0·8-3·3)
Dementia	4	7%	349	8%	1·000	0·88 (0·3-2·5)
COPD	5	9%	240	5%	0·249	1·64 (0·6-4·1)
DM Complicated	8	15%	466	10%	0·371	1·46 (0·7-3·1)
All Diabetes	8	15%	639	14%	1·000	1·0 (0·5-2·1)
Renal Disease	12	22%	771	17%	0·476	1·30 (0·7-2·5)
Age > 60 years	50	91%	4065	91%	0·815	0·98 (0·4-2·5)
BMI > 30kg/m^2	37	67%	2765	61%	0·577	1·19 (0·7-2·1)
Oxygen Saturation < 94%	18	34%	1631	39%	0·670	0·84 (0·5-1·5)
Temperature > 38°C	8	15%	823	20%	0·598	0·75 (0·4-1·6)
MAP < 70mmHg	10	19%	532	12%	0·214	1·57 (0·8-3·1)
D-Dimer > 3 µg/mL	26	55%	1070	30%	0·001	2·81 (1·6-5)
Platelets < 150 $_X10^3$/µL	9	17%	836	19%	0·730	0·83 (0·4-1·7)
INR > 1.2	12	24%	747	18%	0·472	1·31 (0·7-2·5)
BUN > 30 mg/dL	14	30%	1172	29%	1·000	0·98 (0·5-1·8)
Creatinine > 1.5 mg/dL	15	28%	1318	30%	0·659	0·83 (0·5-1·5)
Sodium < 139 or > 154 mEq/L	6	12%	558	13%	1·000	0·87 (0·4-2)
Glucose <60 or > 500 mEq/L	2	5%	104	3%	0·375	1·58 (0·4-6·6)
AST > 40 U/L	26	53%	2001	47%	0·473	1·26 (0·7-2·2)

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			
	Admitted	Deceased	Admitted	Deceased	p value	OR (95%CI)
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 mm^3	<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 mm^3	0.003	1.23	1.1-1.4
AST > 40 U/liter	0.01	1.17	1.0-1.3
BMI > 30 kg/m^2	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
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Jenelys Fernandez-Torres, BA	Montefiore Medical Center	Major Role in acquisition of data
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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

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
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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

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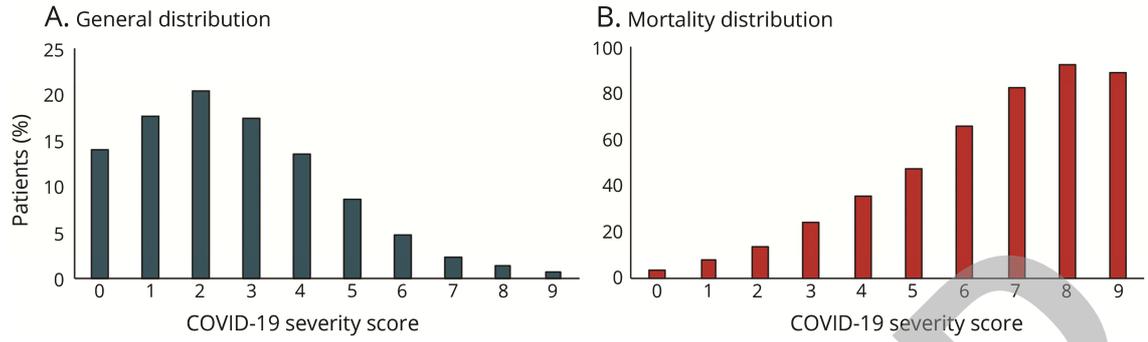
A. General distribution

B. Mortality distribution

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