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Clinical Neurology and Neurosurgery 198 (2020) 106112

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Hemorrhagic presentations of COVID-19: Risk factors for mortality

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ARTICLE INFO

Keywords:
COVID-19
Intracerebral hemorrhage
Subdural hematoma
Outcomes
Subarachnoid hemorrhage
Multi-compartmental hemorrhage
Mortality
SARS-CoV-2

ABSTRACT

Objective: We aim to characterize the incidence, risk for mortality, and identify risk factors for mortality in patients presenting with hemorrhage and COVID-19.

Methods: This retrospective cohort study included a cohort of patients admitted to one of three major hospitals of our healthcare network including, an academic medical center and comprehensive stroke center, which accepts transfers for complex cases from eight community hospitals, during March 1 to May 1, 2020. All patients that received imaging of the neuroaxis and had positive PCR testing for COVID-19 were identified and reviewed by an attending neuroradiologist. Demographics and comorbidities were recorded. Biomarkers were recorded from the day of the hemorrhagic event. Vital signs from the day of the hemorrhagic event mechanical ventilation orders at admission were recorded. Imaging findings were divided into 5 subtypes; acute subdural hematoma (SDH), subarachnoid hemorrhage (SAH), multi-compartmental hemorrhage (MCH), multi-focal intracerebral hemorrhage (MFH), and focal intracerebral hemorrhage (fICH). Outcomes were recorded as non-routine discharge and mortality.

Results: We found a total of 35 out of 5227 patients with COVID-19 that had hemorrhage of some kind. Mortality for the entire cohort was 45.7 % (n = 16). SDH patients had a mortality rate of 35.3 % (n = 6), SAH had a mortality of 50 % (n = 1), MCH patients had a mortality of 71.4 % (n = 5), MFH patients had a mortality of 50 % (n = 2), fICH patients had a mortality of 40 % (n = 2). Patients with severe pulmonary COVID requiring mechanical ventilation (OR 10.24 [.43 − 243.12] p = 0.015), with INR > 1.2 on the day of the hemorrhagic event (OR 14.36 [1.69 − 122.14] p = 0.015], and patients presenting with spontaneous vs. traumatic hemorrhage (OR 6.11 [.31 − 118.89] p = 0.023) had significantly higher risk for mortality.

Conclusions: Hemorrhagic presentations with COVID-19 are a rare but serious way in which the illness can manifest. It is important for neurosurgeons to realize that patients can present with these findings without primary pulmonary symptoms, and that severe pulmonary symptoms, elevated INR, and spontaneous hemorrhagic presentations is associated with increased risk for mortality.

1. Introduction

While pulmonary symptoms secondary to severe acute respiratory syndrome coronavirus 2 (COVID-19) are the most common presentation for the disease, it is now known that a portion of patients develop some degree of neurologic manifestations [1–3]. There have been rare reports of intracerebral hemorrhage in patients with COVID-19 [4,5]. As of now it is unclear how to incorporate COVID-19 diagnosis when making clinical decisions for neurosurgical intervention when patients present with intracranial pathologies while having COVID-19. We aim to review all the cerebral hemorrhage presentations of COVID-19 retrospectively in a large cohort of patients presenting to a large healthcare network at the epicenter of the pandemic, and determine risk factors for mortality within this group.

Abbreviations: COVID-19, severe acute respiratory syndrome coronavirus 2; BMI, Body mass index; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTT, partial thromboplastin time; INR, international normalized ratio; BUN, blood urea nitrogen; SDH, subdural hematoma; SAH, subarachnoid hemorrhage; MCH, multi-compartmental hemorrhage; MFH, multi-focal intracerebral hemorrhage; fICH, focal intracerebral hemorrhage; RT-PCR, reverse transcriptase–polymerase chain reaction

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https://doi.org/10.1016/j.clineuro.2020.106112
Received 30 June 2020; Received in revised form 24 July 2020; Accepted 25 July 2020
Available online 26 July 2020

Table 1
Demographic, clinical, laboratory values and discharge characteristics in patients with brain hemorrhages and COVID-19 positive.

Parameters	All (n = 35)	SDH (n = 17)	SAH (n = 2)	MCH (n = 7)	MFH (n = 4)	Focal ICH (n = 5)
Demographic characteristics						
Age-years, mean (SD)	67.03 (15.5)	77.71 (8.21)	62 (2.83)	63.14 (5.64)	56.75 (24.05)	46.4 (11.35)
Female, n (%)	14 (40)	6 (35.3)	2 (100)	5 (71.4)	0 (0)	1 (20)
Race, n (%)						
White	4 (11.4)	3 (17.6)	0 (0)	0 (0)	1 (25)	0 (0)
African-American	13 (37.1)	5 (29.4)	0 (0)	3 (42.9)	2 (50)	3 (60)
Hispanic	14 (40)	8 (47.1)	1 (50)	4 (57.1)	0 (0)	1 (20)
Other	4 (11.4)	1 (5.9)	1 (50)	0 (0)	1 (25)	1 (20)
BMI, mean (SD)	26.96 (6.13)	22.46 (2.30)	30.95 (1.8)	33.75 (6.07)	30.56 (5.4)	28.18 (4.97)
Severe COVID-19 on admission, n (%)	11 (31.4)	0 (0)	0 (0)	6 (85.7)	3 (75)	2 (40)
Inpatient, n (%)	11 (31.4)	2 (11.8)	0 (0)	5 (71.4)	2 (50)	2 (40)
Emergency, n (%)	24 (68.6)	15 (88.2)	2 (100)	2 (28.6)	2 (50)	3 (60)
Surgical management, n (%)	4 (11.4)	2 (11.8)	1 (50)	0 (0)	0 (0)	1 (20)
Vital signs at admission						
Fever, n (%)	6 (18.2)	3 (17.6)	0 (0)	1 (16.7)	0 (0)	2 (40)
Hypoxemia, n (%)	11 (33.3)	5 (29.4)	0 (0)	4 (66.7)	0 (0)	2 (40)
Systolic blood pressure (mmHg), median (IQR)	130 (113 – 146)	126 (112 – 139)	134.5 (122 – 147)	130 (106 – 158)	154 (113 – 155)	131 (130 – 157)
Diastolic blood pressure (mmHg), median (IQR)	67 (61 – 76)	67 (61 – 88)	68.5 (68 – 69)	63.5 (56 – 74)	67 (65 – 72)	79 (67 – 96)
Comorbidities						
Hypertension, n (%)	25 (71.4)	14 (82.4)	1 (50)	5 (71.4)	2 (50)	3 (60)
Diabetes, n (%)	10 (28.6)	4 (23.5)	1 (50)	5 (71.4)	0 (0)	0 (0)
Congestive heart failure, n (%)	6 (17.1)	4 (23.5)	0 (0)	0 (0)	1 (25)	1 (20)
Myocardial infarction, n (%)	2 (5.7)	1 (5.9)	0 (0)	0 (0)	1 (25)	0 (0)
Chronic pulmonary disease, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any malignancy, n (%)	5 (14.3)	4 (23.5)	0 (0)	0 (0)	1 (25)	0 (0)
Laboratory markers at admission[a]						
WBC count > 10,800 per mm^3	12 (35.3)	4 (23.5)	1 (50)	3 (42.9)	2 (66.7)	2 (40)
Lymphocytes < 1000 per mm^3	20 (58.8)	8 (47.1)	0 (0)	5 (71.4)	3 (100)	4 (80)
Platelets count < 100,000 per mm^3	3 (8.8)	2 (11.8)	0 (0)	1 (14.3)	0 (0)	0 (0)
Alanine aminotransferase > 40 U/L	14 (43.8)	6 (40)	0 (0)	4 (57.1)	0 (0)	4 (80)
Aspartate aminotransferase > 40 U/L	14 (45.2)	7 (50)	0 (0)	4 (57.1)	1 (33.3)	2 (40)
Partial thromboplastin time (PTT) > 38.9 s	6 (20.7)	1 (7.1)	0 (0)	2 (33.3)	2 (66.7)	1 (25)
International normalized ratio (INR) > 1.2	10 (34.5)	10 (83.3)	0 (0)	5 (83.3)	2 (100)	0 (0)
D-dimer > 2 ng/mL	17 (70.8)	12 (100)	1 (100)	6 (100)	3 (100)	3 (75)
Creatinine > 1.33 μmol/L	11 (33.3)	7 (41.2)	0 (0)	2 (33.3)	2 (66.7)	0 (0)
Blood Urea Nitrogen (BUN) > 20 mg/dL	20 (60.6)	11 (64.7)	1 (50)	4 (66.7)	3 (100)	1 (20)
Hemorrhagic etiology						
Traumatic hemorrhage, n (%)	13 (37.1)	12 (70.6)	0 (0)	1 (14.3)	0 (0)	0 (0)
Spontaneous hemorrhage, n (%)	22 (62.9)	5 (29.4)	2 (100)	6 (85.7)	4 (100)	5 (100)
Outpatient medication						
Anticoagulants, n (%)	7 (20)	5 (29.4)	1 (50)	1 (14.3)	0 (0)	0 (0)
Antiplatelets, n (%)	5 (14.3)	3 (17.6)	1 (50)	1 (14.3)	0 (0)	0 (0)
Outcomes						
Non-routine discharge, n (%)	32 (91.4)	14 (82.4)	2 (100)	7 (100)	4 (100)	5 (100)
Mortality, n (%)	16 (45.7)	6 (35.3)	1 (50)	5 (71.4)	2 (50)	2 (40)

[a] Missing values: WBCC 2/35 (5.7 %), Lymphocytes 2/35 (5.7 %), Platelets 2/35 (5.7 %), ALT 3/35 (8.5 %), AST 4/35 (11.4 %), PTT 4/35 (11.4 %), INR 3/35 (8.5 %), D-dimer 9/35 (25.7 %).

2. Methods

2.1. Study design and participants

The data that support the findings of the study are available from the corresponding author upon reasonable request. This retrospective cohort study included a cohort of patients admitted to one of three major hospitals of our healthcare network including, an academic medical center and comprehensive stroke center, which accepts transfers for complex cases from eight community hospitals, during March 1 to May 1, 2020. All patients that received imaging of the neuroaxis were identified and reviewed by an attending neuroradiologist. All patients diagnosed with an intracranial hemorrhage, subdural hematoma, subarachnoid hemorrhage, or multi-compartmental hemorrhage were included in the study. Demographics and comorbidities were recorded (age, gender, race, body mass index (BMI), history of oral anticoagulant use, history of anti-platelet use, hypertension, Diabetes Mellitus, Congestive Heart Failure, Myocardial infarction, chronic pulmonary disease, and malignancy). Biomarkers were recorded from the day of the hemorrhagic event including white blood cell count (WBC), lymphocyte count, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), partial thromboplastin time (PTT), international normalized ratio (INR), D-dimer, creatinine, and blood urea nitrogen (BUN). All laboratory values were categorized for further analyses using the cut-offs stablished by our own institutional protocols. Vital signs from the day of the hemorrhagic event were recorded as well as mechanical ventilation orders at admission. Imaging findings were divided into 5 subtypes; acute subdural hematoma (SDH), subarachnoid hemorrhage (SAH), multi-compartmental hemorrhage (MCH), multi-focal intracerebral hemorrhage (MFH), and focal intracerebral hemorrhage (fICH). Outcomes were recorded as non-routine discharge and mortality. This study was approved by our Institutional Review Board. Patient informed consent was waived. The data that support the findings of the study are available from the corresponding author upon reasonable request.

2.2. COVID-19 screening and diagnosis

Cases were defined as positive by detection of viral RNA using real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay testing, performed within the hospital system or documented at an outside system prior to transfer. Indication for RT-PCR testing was

based on epidemiological risk factors or clinical symptoms suggestive of COVID-19. Patients were tested multiple times with RT-PCR util discharge to evaluate evolution of the disease.

2.3. Statistical analysis

Baseline characteristics between discharged and dead patients, were compared performing parametric and non-parametric analyses with the *t* test, χ^2 test, and Mann-Whitney *U* test as appropriate. No imputation was made for missing data. Our main dependent variable was mortality, potential predictors were analyzed through univariate and multivariate logistic regression controlling for explanatory variables with $p < 0.1$ on univariate analysis. All data analyses were conducted in IBM SPSS (vs26.0, Armonk, NY: IBM Corp).

3. Results

We found a total of 35 out of 5227 patients with COVID-19 that had hemorrhage of some kind. 17 patients presented with SDH, 2 patients with SAH, 7 patients with MCH, 4 patients MFH, 5 patients with fICH. 68.6 % of all these patients presented with primary neurologic symptoms in the emergency room. 31.4 % of these patients acquired these conditions as inpatients. 31.4 % of patients also presented with severe pulmonary COVID symptoms (requiring mechanical ventilation) at admission. A majority of these patients had concomitant intracerebral hemorrhage of some kind (MCH = 85.7 %, MFH = 75 %, fICH = 40 %). None of the subdural or subarachnoid patients had severe pulmonary COVID at presentation. Only 4 (11.4 %) of the cases underwent surgical management. Mortality for the entire cohort was 45.7 % (n = 16). SDH patients had a mortality rate of 35.3 % (n = 6), SAH had a mortality of 50 % (n = 1), MCH patients had a mortality of 71.4 % (n = 5), MFH patients had a mortality of 50 % (n = 2), fICH patients had a mortality of 40 % (n = 2) (Table 1).

Compared to discharged patients, dead patients were mostly represented by Hispanics (56.3 %), had higher rates of severe COVID-19 on admission (10.5 % vs 56.3 %, p = 0.004), higher rates of congestive heart failure (5.3 % vs 31.3 %, p = 0.042), higher rates of prolonged PTT > 38.9 s (0% vs 46.2 %, p = 0.002), higher rates of INR > 1.2 (12.5 % vs 61.5 %, p = 0.006), mostly spontaneous hemorrhages (47.4 % vs 81.3 %, p = 0.039) and lower rates history of anti-platelet use (26.3 % vs 0%, p = 0.027) (Table 2).

Significant variables in the univariate analysis plus variables with P < 0.1 (BMI, systolic blood pressure, any malignancy, ALT > 40U/L and AST > 40U/L) were included in the multivariate logistic regression (Table 3). Patients with severe pulmonary COVID requiring mechanical ventilation (OR 10.24 [.43−243.12] p = 0.015), with INR > 1.2 on the day of the hemorrhagic event (OR 14.36 [1.69−122.14] p = 0.015], and patients presenting with spontaneous vs. traumatic hemorrhage (OR 6.11 [.31−118.89] p = 0.023) had significantly higher risk for mortality.

4. Discussion

Mortality rates for hemorrhagic pathology can vary significantly depending on the type, location, etiology, acuity and severity. Recently mortality rates for subdural hematoma has been shown to be between 12–15 % [6–8]. Intracerebral hemorrhage has a considerably higher case fatality rate from 35 % at 7 days to 59 % at 1 year [9–11]. The impact of COVID-19 on outcomes of patients with brain hemorrhages is unknown. During the pandemic surgical interventions were avoided unless absolutely necessary and as such 1 out of the 4 patients operated on died. Inpatient mortality was considerably higher in all groups of hemorrhage compared to historical norms. In our cohort we found that primary co-presentation of severe pulmonary COVID-19 on admission (OR 10.24 CI [.43−243.12] p = 0.015), an INR > 1.2 (OR 14.36 CI [1.69−122.14] p = 0.015) and spontaneous hemorrhage (OR 6.11 CI

Table 2
Demographic, clinical, laboratory values and discharge characteristics in discharged and dead patients with brain hemorrhages and COVID-19 positive.

Predictors	Discharged	Died	P value
Age-years, mean (SD)	67.16 (16.2)	66.87 (15.15)	0.958
Female sex, n (%)	6 (31.6)	8 (50)	0.268
White	4 (21.1)	0 (0)	0.049[a]
African-American	9 (47.4)	4 (25)	
Hispanic	5 (26.3)	9 (56.3)	
Other	1 (5.3)	3 (18.8)	
BMI	25.38 (4.94)	29.34 (7.15)	0.083[a]
Severe COVID-19 on admission, n (%)	2 (10.5)	9 (56.3)	0.004[a]
Inpatient, n (%)	4 (21.1)	7 (43.8)	0.150
Emergency, n (%)	15 (78.9)	9 (56.3)	
Surgical management, n (%)	3 (15.8)	1 (6.3)	0.377
Fever, n (%)	2 (11.1)	4 (26.7)	0.249
Hypoxemia, n (%)	5 (27.8)	6 (40)	0.458
Systolic blood pressure (mmHg), median (IQR)	140 (124−154)	121 (104−133)	0.073[a]
Diastolic blood pressure (mmHg), median (IQR)	69.5 (65−88)	65 (53−72)	0.126
Hypertension, n (%)	14 (73.7)	11 (68.8)	0.784
Diabetes, n (%)	6 (31.6)	4 (25)	0.668
Congestive heart failure, n (%)	1 (5.3)	5 (31.3)	0.042[a]
Myocardial infarction, n (%)	0 (0)	2 (12.5)	0.112
Chronic pulmonary disease, n (%)	0 (0)	0 (0)	–
Any malignancy, n (%)	1 (5.3)	4 (25)	0.096[a]
WBC > 10,800 per mm^3, n (%)	4 (22.2)	8 (50)	0.126
Lymphocytes < 1000 per mm^3, n (%)	10 (55.6)	10 (62.5)	0.681
Platelets < 100,000 per mm^3, n (%)	1 (5.6)	2 (12.5)	0.476
ALT > 40 U/L, n (%)	5 (29.4)	9 (60)	0.082[a]
AST > 40 U/L, n (%)	5 (29.4)	9 (64.3)	0.052[a]
PTT > 38.9 s, n (%)	0 (0)	6 (46.2)	0.002[a]
INR > 1.2, n (%)	2 (12.5)	8 (61.5)	0.006[a]
D-dimer > 2 ng/mL, n (%)	8 (61.5)	9 (81.8)	0.276
Creatinine > 1.33 μmol/L	4 (22.2)	7 (46.7)	0.138
BUN > 20 mg/dL	10 (55.6)	10 (66.7)	0.515
Traumatic hemorrhage, n (%)	10 (52.6)	3 (18.8)	0.039[a]
Spontaneous, n (%)	9 (47.4)	13 (81.3)	
Hx of Anticoagulants, n (%)	4 (21.1)	3 (18.8)	0.865
Hx of Antiplatelets, n (%)	5 (26.3)	0 (0)	0.027[a]
Hemorrhagic subtypes			
SDH, n (%)	11 (57.9)	6 (37.5)	0.606
SAH, n (%)	1 (5.3)	1 (6.3)	
MCH, n (%)	2 (10.5)	5 (31.3)	
MFH, n (%)	2 (10.5)	2 (12.5)	
Focal ICH, n (%)	3(15.8)	2 (12.5)	

[a] Included in the multivariate analysis.

Table 3
Multivariate logistic regression analysis for mortality in hemorrhagic stroke and COVID-19 positive.

Predictors	Multivariate logistic regression OR [95 % CI] P value
Hispanic vs White	2.9 [.00−4.85] p = 0.954
BMI	.94 [.73−1.2] p = 0.618
Severe COVID-19 on admission	10.24 [.43−243.12] p = 0.015[a]
Systolic blood pressure (mmHg)	.97 [.73−1.2] p = 0.193
Congestive heart failure	4.29 [.09−185.5] p = 0.494
Any malignancy	3.71 [.07−180.5] p = 0.508
ALT > 40 U/L	3.5 [.64−19.2] p = 0.148
AST > 40 U/L	4.45 [.65−30.33] p = 0.128
PTT > 38.9 s	2.04 [.00−20.7] p = 0.99
INR > 1.2	14.36 [1.69−122.14] p = 0.015#
Spontaneous vs Traumatic hemorrhage	6.11 [.31−118.89] p = 0.023#
Hx of Antiplatelets	.01 [.00−.89] p = 0.98

[a] Independent predictors.

[.31 − 118.89] p = 0.023) all carried significantly higher risk for mortality. In our cohort Hispanics had a higher risk of mortality (56.3 %) than other ethnicities (0–25 %).

It is as of yet unknown if there is a causal link of COVID-19 to hemorrhagic pathology of the brain. Severe manifestations of COVID-19 can lead to multi-system organ failure, pro-thrombotic states, cytokine storm, and a form of disseminated intravascular coagulopathy (DIC) which could theoretically predispose to brain hemorrhage [1,12–14]. There are various theories as to potential routes of spread of the virus into the nervous system including hematogenous spread through the blood brain barrier, or a neuronal retrograde neurotropic route through the olfactory tract versus a primary vasculitic response leading to breakdown of the usual blood brain barrier [15,16].

While COVID-19 cannot be directly responsible for traumatic hemorrhage, dizziness and imbalance were common neurologic symptoms seen in COVID-19 patients presenting to our emergency rooms which can predispose to traumatic injury. In Wuhan, dizziness was the most common neurologic symptom seen [1]. In our cohort 0% of our subdural hematoma patients had severe pulmonary symptoms, and a majority (88.2 %) presented to the hospital emergency room with this finding as their presenting illness. As such it is important to note that traumatic subdural hematoma can be a presenting finding of underlying COVID-19 infection. However, we cannot establish if the incidence of dizziness associated to SDH cases or traumatic head injury in general is higher in COVID-19 positive patients due to we did not include COVID-19 negative hemorrhagic cases in our analyses.

Multi-focal and multi-compartmental intracerebral hemorrhage was more likely to present in inpatients (63.6 %) with severe pulmonary COVID-19 infections (81.8 %). The etiology of these hemorrhages is likely multi-factorial secondary to multi-system organ failure, DIC, and iatrogenic use of anti-coagulants. These patients had an extremely poor overall prognosis with a mortality rate of 63.6 %. Unlike intracerebral hemorrhage it does not appear that COVID-19 provokes subarachnoid hemorrhage with the same frequency.

Finally, is worth mentioning that due to our small sample size and limitations inherent to a single center study, these results should be interpreted with caution. Reported rates of mortality in COVID-19 positive patients with hemorrhagic stroke widely varies even within the New York area [17]. Thus, the unique characteristics of our sample such as the high representation of Hispanics and African-Americans combined with the clinical decisions made for each patient might have affected the contribution of risk factors in patients' outcomes; therefore, the predictors for mortality in our study should not be generalized.

Nevertheless, we believe our study provides important data regarding hemorrhagic presentations in COVID-19 patients that will aid to elucidate and contribute to the discussion of how the COVID-19 affects the central nervous system.

5. Conclusions

Hemorrhagic presentations with COVID-19 are a rare but serious way in which the illness can manifest. It is important for neurosurgeons to realize that patients can present with these findings without primary pulmonary symptoms, and that severe pulmonary symptoms negatively effect outcomes.

Disclosures

No relevant disclosures for any of the authors as it pertains to the content of this manuscript.

Sources of support

None.

CRediT authorship contribution statement

David J Altschul: Conceptualization, Supervision, Investigation, Writing - original draft, Writing - review & editing. **Santiago R Unda:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Rafael de La Garza Ramos:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Richard Zampolin:** Conceptualization, Data curation, Methodology, Supervision, Writing - review & editing. **Joshua Benton:** Investigation. **Ryan Holland:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Adisson Fortunel:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Neil Haranhalli:** Conceptualization, Writing - review & editing, Investigation, Visualization.

Declaration of Competing Interest

None of the authors have any conflict of interest as it pertains to the content of this manuscript.

Acknowledgments

In memorium to our beloved colleague James T. Goodrich, MD, PhD who died from COVID-19 during the pandemic of 2020.

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