

## Short Review

### Short Review of “Hemorrhagic Presentations of COVID-19: Risk Factors for Mortality”

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#### Abstract

Coronavirus Disease 2019 (COVID-19) is reported to be associated with a variety of neurological conditions. Altschul et al published an article discussing the presentation of hemorrhagic stroke in COVID-19 positive patients. COVID-19 patients are at an increased risk of mortality from hemorrhagic stroke. Risk factors that may be predictive of mortality are identified. Those risk factors include COVID-19 induced respiratory disease that requires mechanical ventilation, INR lab values greater than 1.2 at the time of presentation and hemorrhages with a sudden, spontaneous onset. Additional papers have been published by other prominent healthcare institutions in the New York City Area which corroborate many of these findings. In this brief review, the original Altschul et al paper and the supporting papers are discussed. In summary, patients with COVID-19 may present with hemorrhagic stroke. Typically, older patients who identify as racial minorities with comorbidities and a severe COVID-19 illness along with abnormal coagulopathies are at an increased risk of mortality.

In July 2020, Altschul et al published an article titled “Hemorrhagic Presentations of Coronavirus Disease 2019 (COVID-19): Risk Factors for Mortality” in *Clinical Neurology & Neurosurgery* [1]. The purpose of this article was to identify predictors of mortality in COVID-19 patients with intracranial hemorrhage.

This study was a retrospective cohort study conducted at the Montefiore health system in the Bronx, NY during the first wave of the COVID-19 pandemic. All patients enrolled in this study were deemed

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to be COVID-19 positive via Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) testing and had neuroimaging performed which showed evidence of an intracranial hemorrhage as diagnosed by an attending neuroradiologist.

Altschul et al. reported the incidence of intracranial hemorrhage in COVID-19 positive patients to be 0.7%. There were five types of intracranial hemorrhage that a patient could present with: Subdural Hemorrhage (SDH), Subarachnoid Hemorrhage (SAH), Focal Intracerebral Hemorrhage (fICH), Multi-Focal Intracerebral Hemorrhage (MFH) and Multi-Compartmental Hemorrhage (MCH). Most patients presented with an intracerebral hemorrhage of some kind (fICH, MFH, MCH). 68.6% of patients were admitted from the Emergency Room (ER) while 31.4% of patients were transferred to the Neurosurgery service from inpatient units. Most of the patients who presented from the ER had primary neurological symptoms while the previously admitted patients had severe pulmonary disease requiring mechanical ventilation. Only 11.4% of patients with an intracranial hemorrhage underwent a surgical intervention. The mortality rate for COVID-19 patients with any kind of intracranial hemorrhage was 45.7%, with the MCH subtype having the highest mortality rate among the five types.

On bivariate analysis, patients with COVID-19 who died as a result of their intracranial hemorrhage were more likely to be Hispanic, have a serious comorbidity like Congestive Heart Failure (CHF), have a more severe COVID-19 course, have prolonged rates of PTT and INR > 1.2 on admission, and mostly presented with spontaneous hemorrhages. On multivariate logistic regression modeling, severe pulmonary COVID-19 disease requiring mechanical ventilation, INR > 1.2 and spontaneous hemorrhage were identified as independent risk factors for mortality.

In the discussion, Altschul et al discuss how the mortality rate for intracranial hemorrhage in COVID-19 patients is far greater than the mortality rate historically reported for this condition in non-COVID patients. This may be explained in part by the decrease in surgical interventions that occurred during the pandemic. Furthermore, the causal link between COVID-19 and a hemorrhagic pathology of the brain is explored. SARS COV-2, the virus that causes COVID-19, may be neurotropic or it may reach the CNS via hematogenous spread and it may lead to an intracranial hemorrhage by inducing a pro-thrombotic state, cytokine storm, or Disseminated Intravascular Coagulopathy (DIC). The different mechanisms that may cause each type of intracranial hemorrhage are also discussed. ICH, especially MFH & MCH are thought to occur secondary to the hematological abnormalities induced by COVID-19 or iatrogenic anti-coagulant use. Subdural hemorrhages can be the result of common neurological symptoms previously reported in COVID-19 patients such as dizziness that may predispose a patient to traumatic injury. For their patient population, Altschul et al reported that the incidence of subarachnoid hemorrhage did not appear to be drastically affected by the COVID-19 pandemic.

Since the publication of this article, additional articles have been published by other healthcare institutions in New York City that corroborate many of these findings. Melmed et al at the NYU Langone Medical Center describe a study with a similar design in an article published in Sept 2020 [2]. They look specifically at non-traumatic Intracerebral Hemorrhages (ICH). They report that older age, non-Caucasian race, severe pulmonary disease requiring mechanical ventilation, and therapeutic anticoagulation are associated with ICH in COVID-19 patients on bivariate analysis. Furthermore, they report that ICH is associated with an increased risk for mortality. Anticoagulant use is identified as the main independent risk factor for ICH and their paper discusses the need to balance the efficacy of anticoagulation in reversing the pro-thrombotic state induced by COVID-19 to prevent thromboembolic complications with the increased risk of hemorrhagic events. In their discussion, they also comment on different mechanisms through which respiratory failure requiring mechanical ventilation that is seen in severe COVID-19 disease may cause ICH. The mechanisms include hypoxia induced blood brain barrier disruption or a hypoxia induced inflammatory response that causes endothelium dysfunction of cerebral blood vessels. In a second paper published in Sept 2020, written by Katz et al. at LIJ Northwell Health, cerebrovascular complications of COVID-19 including intracranial hemorrhages are discussed [3]. This study demonstrates that COVID-19 is an independent risk factor for stroke. They report that while hemorrhagic stroke is less likely to occur than ischemic stroke in COVID-19 patients, any type of intracranial hemorrhage including hemorrhagic conversion of ischemic stroke leads to an increased risk of mortality. Lastly, in a recently published systematic review that includes all studies on the topic of COVID-19 and intracranial hemorrhage from November 2019 to August 2020 [4], the incidence of intracranial hemorrhage in COVID-19 patients is reported to be 0.7% and the mortality rate due to intracranial hemorrhage is reported to be 48.6% which are consistent with the values that Altschul et al reported.

In summary, patients who are COVID-19 positive may present with intracranial hemorrhage, particularly Intracerebral Hemorrhage (ICH). Patients who are older, non-Caucasian, have serious comorbidities at baseline, have a severe respiratory illness caused by COVID-19 requiring mechanical ventilation and are on anticoagulation are at increased risk of mortality. While there are several studies in the literature that support this conclusion, the limitations of these studies include small sample size of each individual study, high false negative rate of COVID test leading to missed COVID-19 patients, patients who either did not undergo imaging or had normal imaging so they were not known to have an intracranial hemorrhage, possible confounders, etc. Additional work needs to be done comparing intracranial hemorrhage in COVID patients with non-COVID patients to prove that a causal relationship exists between COVID-19 and worse outcomes after an intracranial hemorrhage.

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