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Review article

The relationship between COVID-19 infection and intracranial hemorrhage: A systematic review

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ABSTRACT

Introduction: In addition to the deleterious effects Covid-19 has on the pulmonary and cardiovascular systems, COVID-19 can also result in damage to the nervous system. This review aims to explore current literature on the association between COVID-19 and intracranial hemorrhage (ICH).

Methods: We conducted a systematic review of PubMed for literature published on COVID-19 and ICH. Ninety-four of 295 screened papers met inclusion criteria.

Results: The literature addressed incidence and mortality of ICH associated with Covid-19. It also revealed cases of COVID-19 patients with subarachnoid hemorrhage, intraparenchymal hemorrhage, subdural hematomas, and hemorrhage secondary to cerebral venous thrombosis and ischemic stroke. stroke. ICH during COVID-19 infections was associated with increased morbidity and mortality. Risk factors for ICH appeared to be therapeutic anticoagulation, ECMO, and mechanical ventilation. Outcomes varied widely, depending on the severity of COVID-19 infection and neurologic injury.

Conclusion: Although treatment for severe Covid-19 infections is often aimed at addressing acute respiratory distress syndrome, vasculopathy, and coagulopathy, neurologic injury can also occur. Evidence-based treatments that improve COVID-19 mortality may also increase risk for developing ICH. Providers should be aware of potential neurologic sequelae of COVID-19, diagnostic methods to rule out other causes of ICH, and treatment regimens.

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1. Introduction

The 2019 novel coronavirus (Covid-19) pandemic has claimed nearly 5 million lives since it began in November of 2019. Covid-19 infections primarily affect the respiratory system, leading to viral pneumonia via the binding of the SARS-CoV-2 spike protein to the endothelial angiotensin converting enzyme-2 (ACE-2) receptor. However, severe cases of Covid-19 can lead to pathology across multiple organ systems through multiple mechanisms. One mechanism by which multiple organ systems become damaged is related to direct viral invasion, as the ACE-2 receptor is highly expressed in multiple organs, and viral replication itself can cause cell death. A second mechanism is related to the systemic inflammatory response seen in severe cases of Covid-19 caused by cytokine dysregulation, leading to septic shock. Increased vascular permeability and extravasation of both neutrophils and lymphocytes, in combination with viral binding to endothelial cells, can also lead to vasculopathy and vasculitis. The central nervous system (CNS) is one potential target of the Covid-19 virus, and devastating neurologic consequences of infections were reported early in the pandemic. One specific pathology that can lead to these devastating neurologic consequences is intracranial hemorrhage. There has been a higher rate of intracranial hemorrhage associated with Covid-19 than other respiratory viruses, such as the influenza virus (OR 2.85, 1.35–6.02). Further, when patients do suffer intracranial hemorrhage during a Covid-19 infection, they have been shown to be more likely to have a longer length of stay, to require ICU level care, to require mechanical ventilation, and to require vasopressor support. Covid-19 patients that suffer a stroke or intracranial hemorrhage have also been shown to have higher mortality, especially if the patient is on mechanical ventilation.

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Our knowledge and understanding of the pathophysiology of Covid-19 and its treatments is rapidly evolving. However, data on the negative effects that Covid-19 can have outside the respiratory system remains limited, particularly on the devastating consequences it can have on the CNS. Thus, we sought to review the available literature on Covid-19 and its association with intracranial hemorrhage.

2. Methods

The PubMed database was queried using the following search terms: ("subarachnoid hemorrhage") OR ("intraparenchymal hemorrhage") OR ("subdural hematoma") OR ("epidural hematoma") OR ("venous sinus thrombosis") OR ("Sinus thrombosis") AND ("severe acute respiratory syndrome") OR (SARS) OR (SARS-COV) OR ("SARS COV") OR ("novel coronavirus") OR (nCoV) OR ("2019-nCoV") OR (COVID) OR (SARS-CoV-2) OR (COVID-19)). All literature published prior to August of 2021 was then screened (N = 287). Articles were included if they addressed intracranial hemorrhage such as subarachnoid hemorrhage (SAH), intraparenchymal hemorrhage (IPH), subdural hemorrhage (SDH), or hemorrhage related to strokes and venous thrombosis. Articles were excluded if they were not available in English. Eight articles from additional sources were also included to bring the total number of screened articles (either abstract or full text) to 295. All articles were screened by one author (SD), and ninety-four papers were found to meet the inclusion criteria. They were separated into seven sections based on their reported data.

3. Results

Incidence and mortality of intracranial hemorrhage associated with Covid-19

Thirty-three articles were identified in the literature search that reported descriptive statistics on the incidence, distribution, and mortality rates of intracranial hemorrhage in various subgroups of patients with Covid-19 (Table 1).

Five studies reported on these statistics in all hospitalized Covid-19 patients over a defined period of time. The rate of intracranial hemorrhage in this subgroup was reported to be between 0.1% and 3.3% (for patients > 80 years old, the rate was reported at 6.8%). Nine of the studies included information on the distribution of types of intracranial hemorrhage in this population, which included SAH, IPH, intraventricular hemorrhage (IVH), hemorrhagic conversion of ischemic stroke, SDH, and multi-compartment hemorrhage (MCH). In studies with more than one death, the mortality rate for hospitalized Covid-19 with intracranial hemorrhage was reported to be between 50% and 84.6%.

Five studies reported the distribution of types of intracranial hemorrhages in cohorts of patients with Covid-19. SAH and IPH represented the majority of cases in these studies, although SDH and MCH was also reported. Mortality in these cohorts was reported to be between 42.9% and 58%.

There were eight studies that analyzed these statistics in hospitalized Covid-19 patients that had some form of brain imaging. The reported incidence of intracranial hemorrhage in this subgroup was between 2.9% and 11.8%, and was associated with older age, mechanical ventilation, and therapeutic anticoagulation. The mortality of hospitalized Covid-19 patients with intracranial hemorrhage in this subgroup was 29% to 42%.

Four studies included only patients on extracorporeal membrane oxygenation (ECMO) for Covid-19. They reported the rate of intracranial hemorrhage in these patients to be 16% to 42%. Of note, the rate of intracranial hemorrhage in this subgroup of patients is much higher than the rate of cerebral hemorrhage associated with veno-venous ECMO in adults for respiratory failure (3.6%). The reported mortality rate of patients on ECMO for Covid-19 with an intracranial hemorrhage was 75%–82%.

Subarachnoid hemorrhage

There were nineteen studies within the literature search that specifically discussed SAH in patients with Covid-19. One was a large study was done to evaluate the risk of developing SAH during Covid-19 infections by analyzing the de-identified Covid-19 dataset from Cerner. The authors interesting did not find an increased risk of SAH in Covid-19 positive patients compared to Covid-19 negative patients (0.1% vs. 0.2%). However, there was a significantly increased risk of morbidity and in-hospital mortality in Covid-19 positive patients with SAH compared to those without Covid-19 (31.4% vs. 12.2%).

The remaining 18 studies report data on a total of 33 patients, who suffered SAH during Covid-19 infection (Table 2). There were 9 patients who had an aneurysmal SAH, of which at least 4 were asymptomatic from Covid-19. One of the 6 with reported outcomes died. The most common location for the aneurysm was the posterior communicating artery (N = 3). Fourteen patients were reported to have non-aneurysmal spontaneous SAH, of which ten were symptomatic from Covid-19. Five of the 10 patients with symptomatic Covid-19 died. All three with asymptomatic Covid-19 died, and two of the deaths were from subsequent respiratory failure.

One case series is not included in Table 2, because data for the patients is largely aggregated. This case series reports on ten patients with aneurysmal SAH and active or recent Covid-19 diagnosis that presented to one of five cerebrovascular centers over 10 months. Three of the ten patients had severe Covid-19, and four were asymptomatic. Five patients had saccular aneurysms, four had dissecting pseudoaneurysms, and one had a blister aneurysm. Two patients underwent surgical clipping, four underwent aneurysm coiling, three underwent flow diversion, and one patient died prior to treatment. Two of the ten patients died (both had high grade SAH), and seven were discharged with mRS 0–2.

Intraparenchymal hemorrhage

Presentation with Respiratory symptoms

There were nine studies identified that reported information on seventeen patients, who were in the hospital with respiratory symptoms related to Covid-19, and subsequently developed IPH (Table 3). Ten of the seventeen patients were male (58%), and the patients were between the ages of 38 and 74. Thirteen patients were intubated, and four were on ECMO. All seventeen of the patients were on some form of anticoagulation, and thirteen of the seventeen were on therapeutic anticoagulation (76%). The most common type of IPH was unilateral lobar (N = 9), followed by unilateral lobar with intraventricular extension (IVE) (N = 2), bilateral lobar (N = 2), and focal IVE (N = 2, corpus callosum and posterior fossa). One patient had a bilateral lobar IPH with IVE. Mortality was reported in 9 of the 15 patients for whom outcome was reported (mortality rate 60%). Of the six with reported outcome that did not die, two discharged to rehabilitation (one with severe deficits), three had a reported modified Rankin Scale (mRS) of 5, one had a reported mRS of 4.

Presentation with Neurologic symptoms

Five studies were identified that reported information on seven patients, who presented to the hospital with neurologic symptoms related to IPH and were found to have asymptomatic Covid-19 (Table 3). Three patients presented to the hospital with primary
Table 1
Incidence, Distribution, and Mortality of Intracranial Hemorrhage in Covid-19 Patients.

| Study | Population | Incidence | Distribution of Hemorrhage | Mortality |
|-------|------------|-----------|----------------------------|-----------|
| Rothstein, et al.82 | N = 844 | 0.95% | 63% IPH, 37% SAH | 75% (6 of 8) |
| Siegler, et al.90 | N = 14,483 | 0.29% | 47% IPH, 33% Hemorrhagic Conversion, 19% IVH, 17% SAH, 5% SDH | 58.3% (Mortality from Intracranial hemorrhage) |
| Shekhar, et al.88 | N = 90 | 3.3% | 67% IPH with IVE and SAH, 33% SAH | 67% (2 of 3) |
| Kvernland, et al.37 | N = 4071 | 0.8% | 44% Hemorrhagic Conversion, 17% Punctate Hemorrhages, 13% IPH with IVE and SAH, 9% IPH, 9% SAH | 84.6% |
| Sabayan, et al.85 | Physician-reported cases over 1 month in Iran | N = 1 | 100% SAH | 100% (1 of 1) |
| Le, et al.60 | N = 35,177 | 0.5% | 40% SAH, 40% Intracerebral hemorrhage, 20% intracranial hemorrhage | – |
| Katz, et al.49 | N = 10,596 | 0.26% | 50% Intracranial hemorrhage, 39% Combined intracranial hemorrhagic and ischemic stroke, 21% Hemorrhagic conversion, 93% Intracerebral Hemorrhage, 7% SAH | – |
| Shahjouei, et al.50 | N = 17,799 | 0.15% | 80% Intracerebral Hemorrhage, 20% SAH | – |
| Dhamoon, et al.31 | N = 5,469 | 0.3% | 49% SDH, 26% IPH, 20% MCH | 6% SAH |
| Altschul, et al.8 | N = 5,227 | 0.7% | – | – |
| Requena, et al.81 | N = 2,050 | 0.2% | – | 50% (2 of 4) |
| Mao, et al.65 | N = 214 | 0.47% | – | 100% (1 of 1) |
| Nabors, et al.73 | N = 73 (>80 years old) | 6.8% | – | – |
| Cates, et al.26 | N = 3,948 | 0.7% | – | – |
| Chuang, et al.24 | N = 2,414 | 0.1% | – | – |

Symptomatic Intracranial Hemorrhage in Hospitalized Patients with Covid-19

| Nawabi, et al.74 | N = 18 | – | 50% SAH, 33% IPH, 11% IVH, 5% SDH/SAH | 44.4% (8 of 18) |

Covid-19 Positive Patients with Hemorrhage

| Trifan, et al.95 | N = 19 | – | 85% ICH, 15% SAH | 53% (10 of 19) |
| Shahjouei, et al.37 | N = 91 | – | 67% IPH, 25% SAH, 8% MCH | 50% (17 remained in the hospital) |
| Abbas, et al.4 | N = 19 | – | 63% IPH, 31% SAH (21% aneurysmal), 5% SDH | 58% (11 of 19) |
| Ravindra, et al.79 | N = 559 ICH, N = 212 SAH | – | ICH: 46%, SAH: 42.9% | – |

Covid-19 Patients with Brain Imaging

| Kelsch, et al.54 | N = 648 | 3.2% | 38% Hemorrhagic conversion, 29% IPH, 25% SDH, 5% SAH | 42% (6 of 14 with hemorrhagic conversion or IPH) |
| Radmanesh, et al.78 | N = 242 | 2.9% | 57% Chronic Hemorrhage, 29% IPH | 29% |
| Kliironomos, et al.56 | N = 213 | 9% in those with CT, 28% in those with MRI | 14% Hemorrhagic Conversion, 69% IPH, 50% SDH, 31% SAH, 13% EDH | – |

(continued on next page)
| Study                          | Population | Incidence | Distribution of Hemorrhage | Mortality |
|-------------------------------|------------|-----------|-----------------------------|-----------|
| Lang, et al.                  | N = 93     | 11.8%     | 64% ICH                     | –         |
| Mahammedi, et al.             | N = 135    | 10%       | 50% Microhemorrhage         | 29% SAH   |
| Greenway, et al.              | N = 180    | 3.3%      | 67% Intracranial Hemorrhage | 33% Hemorrhagic Conversion | –         |
| Buttner, et al.               | N = 34     | 9%        | –                           | –         |
| Melmed, et al.                | N = 416    | 7.9%      | –                           | –         |
| Covid-19 Patients with Neurologic Manifestations |                       |           |                             |           |
| Varatharaj, et al.            | N = 153    | 5.9%      | –                           | –         |
| Covid-19 Patients on ECMO     |            |           |                             |           |
| Usman, et al.                 | N = 10     | 40%       | 25% IPH                     | 75% (3 of 4) |
| Doyle, et al.                 | N = 51     | 16%       | 88% SAH                     | 12% SDH   |
| Bermea, et al.                | N = 33     | 33%       | –                           | 82%       |
| Masur, et al.                 | N = 12     | 42%       | –                           | –         |

Abbreviations: N = sample size, IPH = Intraparenchymal Hemorrhage, SAH = Subarachnoid hemorrhage, IVE = Intraventricular Extension, IVH = Intraventricular Hemorrhage, SDH = Subdural hematoma, ECMO = Extracorporeal Membrane Oxygenation, ICH = Intracerebral Hemorrhage.

| Study                          | Age, Sex | Aneurysm | Treatment | Outcome                          |
|-------------------------------|----------|----------|-----------|----------------------------------|
| Alam, et al.                  | 38, F    | P-Comm   | Not Reported | Discharged Home                  |
| Rustemi, et al.               | 68, F    | P-Comm (HH1, Fisher II) | Standard of Care | Discharged without deficit   |
| Muhammad, et al.              | 60, F    | Pericallosal (Fisher IV) | Surgical Clipping | Rehabilitation                  |
| Estevez-Ordonez, et al.       | 56, F    | MCA bifurcation (Fisher I) | Surgical Clipping | mRS 1                           |
| Study                         | Age, Sex | Aneurysm  | Treatment | Outcome                          |
| Shojaei, et al.               | 55, F    | A-Comm   | EVD, delayed aneurysm treatment | Death                                      |
| Cezar-Junior, et al.          | 36, F    | Saccular ICA (Fisher IV) | Embolization | mRS 4                           |
| Study                         | Age, Sex | Aneurysm  | Treatment | Outcome                          |
| Swed, et al.                  | 63, M    | Diagnosis | –         | Outcome                          |
| Alam, et al.                  | 41, F    | SAH Description | –         | Outcome                          |
| Haider, et al.                | 56, M    | Bilateral SAH with IVE (unruptured pericallosal aneurysm on cerebral angiography) | Intubated for Neurologic decline | Death due to Respiratory Failure |
| Zulfigar, et al.              | 65, F    | Multifocal SAH | Developed immune thrombocytopenic purpura | Recovered                          |
| Harrogate, et al.             | 74, M    | Multifocal SAH | Intubated | Rehabilitation               |
| Dakhay, et al.                | 53, M    | Bilateral SAH from RCVS | Intubated | Discharged Home               |
| Basirjafari, et al.           | 30's, F  | Diffuse SAH with cerebral edema and no vessel abnormalities | Intubated | Brain Death                |
| Fayed, et al.                 | 54, F    | Diffuse SAH with IVE and sulcal effacement | Intubated | Brain Death                  |
| Mousa-Ibrahim, et al.         | 79, M    | Bilateral cortical SAH and diffuse ischemic injury | Intubated | Brain Death                  |
| Cezar-Junior, et al.          | 53, F    | Fisher III SAH | Intubated | mRS 2                          |
| Abbreviations: M = male, F = female, SAH = Subarachnoid hemorrhage, mRS = modified Rankin Score, P-Comm = Posterior communicating artery, A-comm = Anterior communicating artery, PICA = Posterior inferior cerebellar artery, MCA = Middle cerebral artery, ICA = Internal carotid artery, HH = Hunt Hess, RCVS = reversible cerebral vasoconstriction syndrome.
Intraparenchymal Hemorrhage.

Biopsies

Of note, Anti-SARS-Cov tests were negative on cerebral Covid-19 PCR tests, and subsequently died from IPH after cranial series reported three patients, who had positive pre-operative the patient with the olfactory gyrus hemorrhage recovered. A case the patient with the frontal lobe IPH discharged with mRS 5, and able severity. The patient with the brain stem hemorrhage died, neurologic symptoms, and each was found to have an IPH of vari-

The final study describes a newborn child born at 33 weeks due to pre-term labor, who was found to have bilateral cortical hemor-

Abbreviations: M = male, F = female, IPH = intraparenchymal hemorrhage, IVE = intraventricular extension, mRS = modified Rankin Score, WHO = World Health Organization, DVT/PE = deep vein thrombosis/pulmonary embolism, LMWH = low molecular weight heparin

Table 3

Intracerebral Hemorrhages

| Study                      | Age, Sex | Covid-19 Treatment | Anticoagulation | IPH | Outcome               |
|----------------------------|----------|--------------------|-----------------|-----|-----------------------|
| Ghanilati et al. 25        | 59, F    | Intubated          | Therapeutic Enoxaparin | Frontal IPH with IVE | Brain Death          |
| Charra et al. 23           | 61, M    | Intubated          | Therapeutic Heparin | Corpus Callosum | Not reported          |
| Chalil et al. 22           | 41, F    | Intubated          | Heparin Infusion  | Bilateral Parietal and Occipital IPH with IVE | "severe" deficits |
| Khattar et al. 53          | 43, M    | Intubated          | Heparin Infusion  | Multiloculated IPH in Right Hemisphere | Brain Death          |
| Carroll et al. 19          | 62, M    | Intubated          | Heparin Infusion  | Multilocofal IPH in Left Hemisphere | Brain Death          |
| Fayed et al. 36            | 57, F    | Intubated          | Heparin Infusion  | Right Frontal IPH  | Rehabilitation       |

MOSA-IBRAHIM, ET AL. 70

| Study                      | Age, Sex | Relevant History | Presenting Symptoms | IPH | Outcome               |
|----------------------------|----------|------------------|---------------------|-----|-----------------------|
| Fuji et al. 22             | 54, F    | Post-operative   | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-IBrahim, et al. 70   | 71, F    | Intubated         | Postoperative IPH   | Brain Death |                   |
| Benger, et al. 12          | 41, M    | Intubated         | Frontal Lobe        | mRS 5 | IPH                   |
| Mousa-Ibrahim, et al. 70    | 50, M    | Intubated         | Frontal Lobe        | mRS 5 | Brain Death          |
| Zahid, et al. 102          | 38, M    | ECMO              | Therapeutic Heparin | Small sub-insular IPH | IPH resolved      |
| Engert, et al. 34          | 40, M    | Warfarin          | Dysarthria, Hemiparesis | Frontal Lobe | mRS 5 |
| Flores, et al. 37          | 72, M    | None              | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Benger, et al. 12          | 54, F    | Hypertension, Obesity | Dysarthria, Hemiparesis | Frontal Lobe | mRS 5 |
| Flores, et al. 37          | 40, M    | Hypertension, Obesity | Dysarthria, Hemisensory | Right Temporal Gyrus | Symptoms Resolved  |
| Thu, et al. 24             | 72, M    | On ASA            | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Degeneffe, et al. 30       | 63, M    | None              | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Zahid, et al. 102          | 38, M    | ECMO              | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Zahid, et al. 102          | 54, F    | Post-operative    | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Zahid, et al. 102          | 71, F    | Intubated         | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Zahid, et al. 102          | 52, M    | Intubated         | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Zahid, et al. 102          | 50, M    | Intubated         | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Chalil, et al. 22          | 46, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 54, F    | Heparin Infusion  | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 71, F    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 50, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 50, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 70, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 46, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 50, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 50, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |

Patients Presenting with Neurologic Symptoms

| Study                      | Age, Sex | Relevant History | Presenting Symptoms | IPH | Outcome               |
|----------------------------|----------|------------------|---------------------|-----|-----------------------|
| Chalil, et al. 22          | 54, F    | Warfarin for a history of DVT/PE | Dysarthria, Hemiparesis | Frontal Lobe | mRS 5 |
| Flores, et al. 37          | 40, M    | Hypertension, Obesity | Dysarthria, Hemiparesis | Frontal Lobe | mRS 5 |
| Thu, et al. 24             | 72, M    | None              | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Degeneffe, et al. 30       | 63, M    | On ASA            | Seizures, Loss of Smell | Right Temporal Gyrus | Symptoms Resolved  |
| Chalil, et al. 22          | 46, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 54, F    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 71, F    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 50, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Zahid, et al. 102          | 38, M    | ECMO              | Therapeutic Heparin | Small sub-insular IPH | IPH resolved      |
| Czech, et al. 33           | 54, F    | Intubated         | Thrombocytopenia     | Brain Death |                   |
| Mousa-Ibrahim, et al. 70    | 71, F    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 52, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |
| Mousa-Ibrahim, et al. 70    | 50, M    | Prophylactic LMWH | Frontal Lobe        | mRS 5 | Brain Death          |

Abbreviations: M = male, F = female, IPH = intraparenchymal hemorrhage, IVE = intraventricular extension, mRS = modified Rankin Score, WHO = World Health Organization, DVT/PE = deep vein thrombosis/pulmonary embolism, LMWH = low molecular weight heparin

Subdural hematoma

Two patients were identified in two separate articles that suffered a SDH during a Covid-19 infection. The first was in a case report of a 50-year-old Covid-19 positive male admitted for treatment of newly diagnosed acute promyelocytic leukemia, who developed an acute SDH with 12 mm of midline shift. He underwent decompressive craniotomy and passed away after surgery due to disseminated intravascular coagulopathy (DIC). The authors concluded that the SDH would have been unlikely without a simultaneous diagnosis of Covid-19. The second case was identified in a single institution case series of Covid-19 patients with a devastating neurologic outcome. This patient was a 68-year-old female, who was incidentally found to be Covid-19 positive, and presented with a spontaneous SDH, requiring neurosurgical decompression. She suffered a post-operative IPH likely due to a cortical vein thrombosis, but she was eventually discharged to rehabilitation.

Multicompartment Hemorrhages

Five studies reported on eight Covid-19 patients, who developed simultaneous MCH (Table 4). Seven of the 8 patients presented with respiratory symptoms. Within that group, five were male, and they were all between the ages of 59 and 76. Five of...
### Table 4
Multicompartment Hemorrhages.

| Study                        | Age, Sex | Primary Symptoms | Anticoagulation                                                                 | Bleed                                                                 | Outcome                      |
|------------------------------|----------|------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------|
| Gogia, et al.40              | 75, M    | Respiratory      | Aspirin, Clopidogrel, therapeutic enoxaparin                                   | - SDH                                                                | Brain Death                   |
|                              |          |                  |                                                                                 | - Temporal IPH (100 mL)                                              |                               |
|                              |          |                  |                                                                                 | - SAH                                                                |                               |
| Al-Olama, et al.5            | 36, M    | Neurologic (Covid-19 RNA in CSF) | –                                                                                  | - IPH                                                                | Surgical Decompression        |
|                              |          |                  |                                                                                 | - SAH                                                                |                               |
|                              |          |                  |                                                                                 | - Small SDH                                                           |                               |
| Ghani, et al.38              | 59, M    | Respiratory      | –                                                                                  | - IPH (posterior fossa)                                              | Brain Death                   |
|                              |          |                  |                                                                                 | - SAH                                                                |                               |
|                              | 61, F    | Respiratory      | –                                                                                  | - SAH                                                                | Brain Death                   |
|                              |          |                  |                                                                                 | - Diffuse SAH                                                        |                               |
| Soldatelli, et al.91         | 67, M    | Respiratory      | Prophylactic Enoxaparin                                                         | - IPH with IVE                                                       | Rehabilitation                |
|                              |          |                  |                                                                                 | - Corpus Callosum Microbleeds                                        |                               |
|                              |          |                  |                                                                                 | - SAH                                                                |                               |
|                              | 71, F    | Respiratory      | –                                                                                  | - SAH                                                                | Rehabilitation (mRS 4)        |
| Mousa-Ibrahim, et al.70       | 76, M    | Respiratory      | Therapeutic LMWH                                                               | - IPH with IVE                                                       | Brain Death                   |
|                              |          |                  |                                                                                 | - SAH                                                                |                               |
|                              |          |                  |                                                                                 | - Cerebellar IPH                                                     |                               |
|                              |          |                  |                                                                                 | - (1.3 cm MLS)                                                       |                               |
|                              | 63, M    | Respiratory      | Therapeutic LMWH                                                               | - Bilateral IPE with IVE                                            | Brain Death                   |
|                              |          |                  |                                                                                 | - SAH                                                                |                               |
|                              |          |                  |                                                                                 | - Parietal infarct with hemorrhagic conversion                      |                               |

Abbreviations: M = male, F = female, RNA = ribonucleic acid, CSF = cerebral spinal fluid, SDH = subdural hematoma, IPH = intraparenchymal hemorrhage, SAH = subarachnoid hemorrhage, IVE = intraventricular extension, mRS = modified Rankin Score

### Table 5
Hemorrhages associated with Cerebral Venous Thrombosis.

| Study                        | Age, Sex | Presenting Symptoms | Anticoagulation at the time of CVT | CVT | Hemorrhage | Outcome                  |
|------------------------------|----------|---------------------|------------------------------------|-----|------------|--------------------------|
| Keaney, et al.51             | 51, M    | Respiratory (Intubated) | Dual antiplatelet therapy and anticoagulation | Superior Sagittal Sinus | Hemorrhagic Infarction  | Brain Death               |
| Thompson, et al.93           | 50, M    | Respiratory (Intubated) | Prophylactic enoxaparin            | Superior Sagittal Sinus | Hemorrhagic Infarction  | Brain Death               |
| Ren, et al.30                | 53, F    | Respiratory         | Unknown                            | Cortical Venous Thrombosis | IPH                  | Rehabilitation            |
| Bolaji, et al.55             | 65, M    | Neurologic (hemiparesis) | None                              | Superior Sagittal, Right transverse, Right sigmoid sinus | Lobar IPH | Discharged                |
| Hussain, et al.46            | 30, M    | Neurologic (Seizure) | None                               | Torcular, Transverse sinus, Sagittal sinus | Spontaneous SDH | Discharged                |
| Luzzi, et al.62              | –        | Neurologic          | None                               | Transverse and Sigmoid Sinus | Bilateral IPH | Remains hospitalized (improving) |
| Loos, et al.61               | 44, F    | Neurologic          | None                               | Inferior Sagittal Sinus, Straight sinus, Internal cerebral veins, Vein of Rosenthal, | Sulcal SAH | Rehabilitation            |
| Beretta, et al.13            | 62, F    | Neurologic          | None                               | Superior Sagittal Sinus, Straight Sinus, Transverse sinus, Vein of Galen, Bilateral internal cerebral veins | Occipital IPH | Discharged without deficit |
| Bastidas, et al.47           | 13, F    | Neurologic (Headache, vomiting) | None                              | Bilateral transverse sinus and Right sigmoid sinus | Hemorrhagic infarct | Discharged with neurologic deficits |
| Klein, et al.55              | 29, F    | Neurologic (Seizure) | None                               | Transverse and Sigmoid Sinus | Hemorrhagic infarct | Recovered                |
| Hemasian, et al.45           | 65, M    | Neurologic          | None                               | Transverse and Sigmoid Sinus | Lobar IPH | Brain Death after Neurosurgical decompression |
| Tu, et al.56                | 30’y M   | Neurologic (Seizure) | None                               | Transverse and Sigmoid Sinus | Brain Death |                               |
those patients died (mortality rate 71%), and two were discharged to rehabilitation. Of those with primary respiratory symptoms, four were on some form of anticoagulation and/or antiplatelet medications. The most common combination of hemorrhages was IPH/SAH (N = 4), followed by IPH/SAH/SDH (N = 2) and SAH/SDH (N = 1).

One patient (36-year-old male) presented primarily with neurologic symptoms and was found to have a multicompartment hemorrhage (IPH/SAH/SDH). He required neurosurgical decompression, and Covid-19 RNA was present in his cerebrospinal fluid (CSF). His outcome was not reported.

Hemorrhage related to cerebral venous thrombosis

There were 16 studies identified that included a total of 17 patients with either active or recent Covid-19 infection, who had cerebral venous thrombosis (CVT) associated with intracranial hemorrhage. There were also three large studies discovered by the search that reported statistics on patients with Covid-19 and cerebral venous sinus thrombosis (CVST). One study was done over nine months and identified eight patients that met this inclusion criteria, of which 2 had associated intracranial hemorrhage (25%). The authors also conducted a literature review on this topic and reported that 6 of the 33 patients identified in the literature had an associated intracerebral hemorrhage (18%). Another study conducted across three academic centers identified six patients with Covid-19 and CVST, of which four had associated hemorrhagic parenchymal lesions (66.7%). The third study was done across nine tertiary care stroke centers and identified 13 patients with Covid-19 and CVST, of which four had associated IPH (31.7%).

Of note, the authors of that article report that this is the same rate of associated hemorrhage in a historical group of patients with CVST.

Patients with active Covid-19 infection

The literature search identified 12 studies with 13 patients, who had active Covid-19 infection and developed an intracranial hemorrhage related to a CVT (Table 5). The patients ranged in age from 13 to 75 years old, and 50% (6 of 12) were female. Four patients were in the hospital for respiratory symptoms related to Covid-19, of which three were intubated for respiratory failure. The remaining nine patients presented with neurologic symptoms and were found to have asymptomatic Covid-19. None of the patients that presented with neurologic symptoms were reported to be on anticoagulation. The most common thrombosis was found in the transverse and sigmoid sinus (N = 6), followed by superior sagittal sinus (N = 2), and the superior sagittal sinus extending to the transverse and sigmoid sinuses (N = 2). The most common associated hemorrhage was IPH (N = 6), followed by hemorrhagic infarct (N = 4).

Patients with recent Covid-19 infection

There were four studies that each reported on a single patient with a recent Covid-19 infection, who subsequently presented with CVT and associated intracranial hemorrhage (Table 5). All four were male patients, and they were between the ages of 27 and 57 years old. One patient had isolated cortical vein thrombosis, and the other three patients had sinus thrombosis. They presented

Table 5

| Study                  | Age, Sex | Presenting Symptoms | Anticoagulation Infarcted Area | Hemorrhage | Outcome          |
|------------------------|----------|---------------------|--------------------------------|------------|------------------|
| De Castillo, et al. 29  | 64, M    | None (presented with neurologic symptoms) | Thalamic and Temporal/Occipital lobe | Parietal SAH | Discharged (mRS 4) |
| Kaushik, et al. 50      | 5, M     | Therapeutic anticoagulation for ECMO | ACA and MCA territory infarct | SAH | Brain Death |

Table 6

| Study                  | Age, Sex | Anticoagulation | Hemorrhagic Conversion of Ischemic Stroke Infarcted Area | Hemorrhage | Outcome          |
|------------------------|----------|----------------|--------------------------------------------------------|------------|------------------|
| Melegari, et al. 67     | 55, F    | Prophylactic LMWH | Temporal and Parietal lobe | Occipital and Temporal Lobe | Brain Death |
| Vacaras, et al. 28      | 50, M    | Had been on Prophylactic Enoxaparin | Multifocal in Bilateral Hemispheres | Multifocal with SAH | Discharged Home |
| Fayed, et al. 36        | 71, M    | None | Occipital Lobe | Occipital Lobe | Death from Multi-organ failure secondary to DIC |

Abbreviations: CVT = cerebral venous thrombosis, M = male, F = female, IPH = intraparenchymal hemorrhage, SAH = subarachnoid hemorrhage, SDH = subdural hematoma.
2–4 weeks following a Covid-19 infection, and all four patients recovered.

**Hemorrhage related to ischemic stroke**

**Simultaneous ischemic stroke and intracranial hemorrhage**

There were five studies that described Covid-19 positive patients with simultaneous ischemic stroke and intracranial hemorrhage, four of which reported the incidence (Table 6). A large retrospective study across 11 New York hospitals looked at the rate of hemorrhagic conversion after ischemic stroke in 10,596 hospitalized Covid-19 patients. They reported that 86 (0.81%) had an ischemic stroke, and that eight of those patients had evidence of simultaneous hemorrhage (0.08%). A second study from a single New York stroke center prospectively followed eight hospitalized Covid-19 patients with ischemic stroke and reported that two had an associated intracranial hemorrhage (25%). Both patients had SAH secondary to cerebral artery dissection, and neither patient had any known risk factors. The third study reported that symptomatic Covid-19 patients with an ischemic stroke had a higher rate of associated intracranial hemorrhage than asymptomatic Covid-19 patients with ischemic stroke (31.7% vs. 4.4%).

The remaining two studies reported two cases of Covid-19 patients with simultaneous intracranial hemorrhage and ischemic stroke (Table 6). One was a 64-year-old Covid-19 positive male that presented with neurologic symptoms and was found to have ischemic strokes in the thalamus, temporal lobe, and occipital lobe. He had an associated SAH and was discharged home. The second was in a 5-year-old male on ECMO for Covid-19, who developed a large infarct in the ACA and MCA territory. He had an associated SAH and progressed quickly to brain death.

**Hemorrhagic Conversion of Ischemic Stroke**

The search resulted in six studies discussing hemorrhagic conversion of ischemic stroke in patients with Covid-19, three of which analyzed the incidence of these bleeds (Table 6). The large retrospective study mentioned in the previous section of 10,596 hospitalized Covid-19 patients reported that of the 86 with an ischemic stroke, six had evidence of hemorrhagic conversion (0.06%). The second study included 34 S centers in Europe, and reported data on 93 Covid-19 patients, who underwent mechanical thrombectomy for large vessel occlusions. Of those 93 patients, 23 (25%) had intracranial hemorrhage conversion within 30 days of MT, and five (5%) were symptomatic. The third study was a case series of 22 Covid-19 patients with acute cerebrovascular disease. They reported that three of the 22 (13.6%) suffered hemorrhagic conversion, and all required neurosurgical decompression.

The remaining three studies describe three total cases of Covid-19 patients, who suffered hemorrhagic conversion of an ischemic stroke (Table 5). Two patients were intubated for Covid-19 at the time, and one presented with neurologic symptoms two days after being discharged. One patient was on prophylactic anticoagulation at the time of the stroke. One patient died from the stroke, and one patient died from multi-organ failure related to disseminated intravascular coagulation.

**4. Discussion**

This article provides a systematic review of nearly 100 PubMed indexed articles on the association between Covid-19 and intracranial hemorrhage. Among all hospitalized Covid-19 patients, the rate of intracranial hemorrhage is reported here to be between 0.1% and 3.3%, and it likely increases for patients 80 years old. The data reviewed here suggests that the development of an intracranial hemorrhage during Covid-19 infection is associated with increased rates of morbidity. These patients have a longer length of hospital stay, are more likely to require ICU level care, are more likely to have longer lengths of ICU stay, are more likely to require mechanical ventilation, and are more likely to require vasopressor support. They also have an exceptionally high mortality rate, which is reported in articles included here to be 42–84%.

Nearly all subtypes of intracranial hemorrhage were represented in this literature review, including SAH (both aneurysmal and spontaneous), IPH, SDH, MCH, hemorrhage related to cerebral venous thrombosis, simultaneous hemorrhage with ischemic stroke, and hemorrhagic conversion of ischemic stroke. This suggests that although Covid-19 is associated with an increased risk of intracranial hemorrhage, there does not appear to be a predisposition for a specific subtype of hemorrhage. This also serves to highlight the point that not all intracranial hemorrhage during Covid-19 infection can be attributed to the pathology of the virus. It remains critically important to rule out other etiologies of intracranial hemorrhage in these patients, such as aneurysms, vascular malformations, underlying lesions, and underlying coagulopathy, in order to provide appropriate treatment.

The risk factors for developing an intracranial hemorrhage during a Covid-19 infection include therapeutic anticoagulation and mechanical ventilation. There also appears to be an increased rate of mortality for patients who develop an intracranial hemorrhage while on ECMO for Covid-19. Unfortunately, these risk factors may be necessary treatment modalities for Covid-19 infections. Mechanical ventilation and ECMO are often employed in Covid-19 due to acute respiratory distress syndrome, and therapeutic anticoagulation has been shown to improve outcomes in non-critically ill Covid-19 patients. Thus, when caring for Covid-19 patients, careful consideration of the nuanced risks and benefits of these various treatment modalities is clearly necessary.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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