COVID-19 infection and survival in patients with spontaneous intracerebral haemorrhage

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Spontaneous intracerebral haemorrhage in patients with COVID-19 infection can negatively affect their clinical outcome. From an overview of the current literature, the most common reported comorbidities were hypertension, diabetes, and cardiovascular disease. A Glasgow Coma Scale (GCS) < 8 at presentation affects clinical outcome in all patients; however, it seems that mortality for intracerebral haemorrhages in patients with COVID-19 infection is higher (consistent in more than half of patients) than patients without infection. Published data support accumulating evidence that patients with COVID-19 infection tend to develop extensive intracerebral haemorrhages that can increase in size more quickly than usual and lead to deadly bleeding.

The current COVID-19 pandemic caused by SARS-CoV-2 has spread worldwide with over 47.000.000 reported cases. Patients typically present with fever, shortness of breath and cough. In addition, some patients with COVID-19 presented neurologic manifestations, such as headache, loss of sense of smell, stroke and seizures, suggesting that SARS-CoV-2 displays neurotropism and enters the central nervous system (1-3). Some of these neurological symptoms, like headache and fatigue, were related to COVID-19 infection, as they are flu-like symptoms. However, more severe neurological symptoms can be related to more severe intracranial diseases like ischemic stroke, spontaneous intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH) due to aneurysms or other arteriovenous malformations.

Keywords: COVID-19; intracerebral haemorrhage; intraparenchymal haemorrhage; overall survival;

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It is reported that when ICH occurs in patients with COVID-19 infection, the diagnosis results are more challenging to reach, especially in patients with ARDS, which require endotracheal intubation and neurological examination is more challenging to do (2, 3). ICH has a mortality rate of almost 50% when associated with intraventricular haemorrhage within the first month and an 80% dependency rate at 6 months from onset (4). ICH itself can negatively affect the clinical outcome of patients with laboratory-confirmed COVID-19 infection, as often they are old and present several comorbidities. Furthermore, severe COVID- 19 infection can lead to critical illness as ARDS and multi-organ failure as its primary complications, eventually followed by intravascular coagulopathy (5), that can worsen the initial neurological clinical presentation. Continuous observation and daily clinical practice by physicians and surgeons and scientific published research can improve long-term all patient outcomes (6-36).

From an overview of the current literature, the most common reported onset symptoms in patients with Covid-19 are fever, cough, myalgia, or fatigue (37,38). Neurologic manifestations in patients with COVID-19 are common too (39-41). The occurrence of a broad spectrum of neurologic complications in hospitalized patients with laboratory-confirmed COVID-19 infection supports the possible neuroinvasive potential of SARS-CoV-2 (3). However, a direct link between neurological symptoms and the clinical condition cannot be drawn at the current state of knowledge. Zhou *et al.* (42) confirmed that COVID-19 uses the same receptor for cell entry as other coronaviruses, ACE2.

ACE2 has been demonstrated to be expressed in neurons and endothelial and arterial smooth muscle cells in the brain (43), potentially allowing SARS-CoV-2 to cross the blood-brain barrier and affect the CNS. Published papers (37, 44) on COVID-19 infection postulated that cerebrovascular diseases resulted from a cytokine storm during the infection, as monocytes and tissue cells activated, causing the release of cytokines and the expression of cytokines tissue factors, which led to altered coagulation activity. It is difficult to ascertain that all ICHs reported were directly related to the COVID-19 infection; however, it is possible that in those patients without any significant risk factors or comorbidity, the cytokine storm, coupled with the sympathetic drive-in attempt to combat the infection, may have had a role in the development of ICH. Platelet count is a simple and readily available biomarker, independently associated with disease severity and risk of mortality in the ICU (45,46). Lippi *et al.* (5) investigated if thrombocytopenia may be associated with severe COVID-19, concluding that low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19.

As other cases with isolated severe thrombocytopenia in patients with COVID-19 infections were reported (47,48), some patients developed severe immune thrombocytopenia due to COVID-19 infection and subsequently had ICH due to coagulopathy. Some patients with COVID-19 infection underwent extracorporeal membrane oxygenation, which required therapeutic anticoagulation to maintain therapy but predisposed patients to additional bleeding complications (49,50,51). Recent studies (37,52) showed that up to 20% of COVID-19 patients have abnormal coagulation function and that COVID-19 infection could also manifest in significant abnormal coagulation parameters, notably more prolonged PT and aPTT. Another study involving 1099 patients showed that 82.1% of patients had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia (53). Due to the high tendency of patients with COVID-19 infections to develop alteration in coagulation, the surgical outcome for ICH of those patients will be poor.

It is common to find that ICHs occurred in intubated patients due to COVID-19 breathing difficulties or ARDS. These patients were difficult to evaluate neurologically and, in these patients, ICHs were often detected with CT scans performed after nonreactive fixed and dilated pupils had been observed. Other clinical symptoms reported were loss of consciousness, headache and hemiparesis and GCS at presentation was higher than 12 only in 21.1% of patients (1). Hypertension and cardiovascular disease, comorbidity associated with a worse health outcome, more complex clinical management and increased health care in patients with COVID-19 infections were

present in 54.4% and 20% of patients, respectively (1). Jain *et al.* (54) also reported in their study that COVID-19 patients who had sizeable ischemic stroke or ICHs on imaging have a 50% mortality. Zhou *et al.* (55) concluded that ICH in admitted COVID-19 patients is one of the most substantial prognostic factors of poor outcome, even more than age and other previously reported comorbidities such as hypertension and obesity.

These data support accumulating evidence that patients with COVID-19 infection tend to develop large ICHs that can increase in size more quickly than usual and lead to deadly bleeding. In addition, patients with COVID-19 infection could develop ICHs that are difficult to treat surgically due to coagulation abnormalities and a high risk of rebleeding. We cannot speculate on ICH incidence in patients with COVID-19 infections; however, ICHs in patients with COVID-19 infection increase the risk of mortality in these patients (56-117). The ICHs and COVID-19 infection pathophysiology is still under investigation and warrants additional studies.

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