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**Research Paper**

# Intracerebral Hemorrhage in COVID-19: A Case Series Study

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**ABSTRACT:**

**BACKGROUND**:

Beyond pulmonary infection, SARS-CoV can cause dysfunction of multiple organs and systems. Cardiovascular complications after COVID-19 have now been reported very often but the knowledge of neurovascular complications especially Intracerebral Hemorrhage (ICH) is undetermined. Overall it is well-documented complication of COVID-19**.**

**OBJECTIVE:**

To describe the natural history of acute Intracranial Hemorrhage (ICH) in COVID-19 patients.

**PATIENTS AND METHODS:**

A case series study was performed at Al-Imamain Al-Kadhimain medical city and Saad Alwitry Hospital for Neuroscience in 2021.

**RESULTS:**

Twenty patients with ICH were included in this study, 12 (60%) participants were males while females were 8 (40%) participants with mean age of 54.38±10.51 years; 10 (50%) patients had high systolic and diastolic blood pressure on presentation with preexisted hypertension and /or diabetes. The most prevalent comorbidities were Hypertension and Diabetes mellitus. The maximum duration between initial infection and presentation of ICH was 30 days in both males and females ranging between 5 and 30 days. Regarding the site of involvement (50%) of patients presented with cerebral hemisphere (deep-seated) involvement on CT scan and 3 (15%) of deep-seated developed intraventricular extension and 3 (15%) had lobar presentation. Cerebellar, brainstem, and SAH were the least site of presentation with 10%, 5%, and 5%, respectively. According to lab investigation, 13 out of 20 patients (70%) in the present series had positive PCR with variable IgM and IgG results, but almost all of them had abnormal D-dimer, CRP, and S. ferritin with mean 1208, 27, 453 respectively. Almost all of the patients had normal Hb and platelet levels, with a mean of abnormal neutrophil (77) $10^9$/L, and (16) $10^9$/L lymphocyte count.

**CONCLUSION:**

This study provides evidence of ICH in the middle-aged patients demographic, a deep-seated predominance, and a marked systemic inflammatory prodrome. SARS-Covid-19 increases the preexistence risk such as HTN, DM, and the ICH cannot be attributed solely to COVID-19 itself.

**KEY WORDS:** Severe acute respiratory syndrome coronavirus, Intracerebral hemorrhage, Subarachnoid hemorrhage.

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## INTRODUCTION:

This paper aims to prove that COVID-19 infection predisposes to Intracerebral hemorrhage.

The coronavirus disease 2019 (COVID19) devel oped when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-

2) infection emerged in Wuhan, China, in Decem ber 2019, affecting the community's relations as well as the health system. In addition to pulmonary infection, SARS-CoV can lead to many organ and system dysfunctions [(1)].

The infection's clinical spectrum varies from pneumonia with no symptoms to severe pneumonia that requires hospitalization to an intensive care unit. Although there is little evidence linking SARS-CoV-2 sequelae to cardiovascular disease, earlier studies from the 2003 SARS outbreak in Asia indicated a higher prevalence of thromboembolic consequences, such as stroke.

A better characterization of complications associated with COVID-19 infection is important

to guide decision-making [2]. Neurological problems, such as gustatory, olfactory abnormalities and encephalitis, are particularly common in elderly people with chronic medical conditions. This suggests that the virus may be able to enter the brain and affect the nervous system. Furthermore, afflicted patients may experience emotional stress due to COVID-19 infection [3].

The neurologic symptoms of COVID-19 can be separated into two groups: post-viral symptoms that appear after the acute phase of the infection, known as post-acute phase complications [4], and those that happen during the acute phase of the infection, known as Para-infectious complications.

Hemorrhagic and ischemic strokes have been reported and are taken into account when evaluating COVID-19 patients who have established vascular risk factors [5]. Although it is uncommon, intracerebral hemorrhage (ICH) has been reported as a COVID-19 complication. Primary ischemic stroke (ICH) can happen with or without established risk factors like anticoagulant therapy (COVID-19 thrombo-prophylaxis or pre-treatment of unrelated disease) [6]. Brain haemorrhage can be caused by cerebral sinus thrombosis; ICH can be related to the hemorrhagic transformation of an acute ischemic stroke or problems from revascularization treatments [8].

Hemiparesis, headaches, eye deviations, and impaired level of consciousness are common symptoms seen in patients with ICH. Computed tomography (CT) scans are required and can be done quickly to differentiate between ischemic stroke and ICH. CT angiography is a highly specific test and is suitable for finding the bleeding source. Other options include brain magnetic resonance imaging and angiography [9].

Several Covid cases have the potential to cause disease via a variety of organ systems and pathways. One mechanism is damage to multiple organ systems that are related to invasion of the virus, as the ACE-2 receptor that is highly expressed in multiple organs, and replication of the virus cause the cell death [12]. A second mechanism is related to the systemic inflammatory response can been seen in severe cases of Covid-19 caused by cytokine dysregulation, leading to septic shock. Vasculopathy and vasculitis can also result from increased vascular permeability, neutrophil and lymphocyte extravasation, and viral binding to endothelial cells. The final mechanism that Covid-19 can damage several organ systems is through Covid-19-associated coagulopathy (CAC). Elevations of fibrinogen and D-dimer are indicative of CAC, which causes parenchymal hemorrhage as well as vascular thrombosis [12,13].

Similarities exist between SARS-CoV-2 and SARS-CoV, and both anecdotal and statistical data indicate that neurological symptoms are uncommon in COVID-19 patients. Based on available data, hemorrhagic stroke may occur more frequently as a result of SARS-CoV-2 infection, particularly in persons who are already at risk. Viral infections of the central nervous system have the potential to compromise the neurovascular and cause cerebral haemorrhage [13].

The Study aims to describe the natural history of acute Intracranial Hemorrhage (ICH) in COVID-19 patients.

## PATIENTS AND METHODS:

A case series study, performed at Al-Imamain Al-Kadhimain medical city and Saad Alwitry Hospital for Neuroscience during 2021. Twenty (20) patients diagnosed with ICH after COVID-19 infection were recruited to the study, with complete information and follow-up regarding timing, diagnosis, and natural history of the phenomenon.

Cases with covid19 infection documented to have ICH after the infection were included in the study with the exclusion of Cases of secondary ICH from a hemorrhagic transformation of ischemic stroke, patients using anticoagulants, patients with brain tumors, vascular aneurysm, cerebral malformation, and patients with any missing information in his history or investigation.

A modified structure questionnaire paper that referenced a published article (Coronavirus disease 2019 can predispose young to ICH) and modified by the researcher and approved by the supervisor was filled by the researcher with direct interview. It includes the following data:

1. Sociodemographic, Risk factors (Age, gender, personal phone number, history of chronic diseases, smoking history, blood pressure at time of presentation).
2. The duration between COVID infection and the development of ICH
3. Investigations: PCR results, Rapid test (IgG, IgM), CRP, D-dimer, Ferritin, CBC.
4. Location of hematoma.
5. The severity of COVID-19 infection was determined in our study according to the clinical criteria based on World Health Organization (WHO) to mild, moderate, severe, and critical illness [16].

Mild: Symptomatic individuals who fulfil the COVID-19 case description but don't have hypoxia or pneumonia symptoms.
Moderate: is characterised by fever, cough, dyspnea, and rapid breathing, although it does not exhibit severe symptoms such as blood oxygen saturation ($SpO_2$) levels ≥90% on room air.
Severe: one of the following plus the clinical indications of pneumonia (fever, cough, dyspnea, rapid breathing) breathing more quickly than thirty breaths per minute, experiencing severe respiratory distress, and having a $SpO_2$ below 90% when breathing on room air.
Critical disease: the presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, acute thrombosis, or multisystem inflammatory syndrome.
Approvals of the committee of the Iraqi Board of Medical Specializations and Al-Karkh and Al-Rasafa health directorate were obtained before the study start. The administration of both hospitals was informed about the nature, scope of the study and verbal consent was obtained from them. Information will be kept private and used only for the intended purpose of the study.
Microsoft Excel 2010 and IBM SPSS version 24 were used for data entry, management, and analysis. Descriptive statistics of the variables were expressed as percentages and Mean±SD. The $X^2$ test was used to test for associations between variables. P value at < 0.05 was considered to be significant.

## RESULTS:

Demographic, Clinical, Laboratory and Image Characteristics of the Study population:
Twenty patients with ICH were included in this study, found to have concurrent confirmed COVID-19 during the last month and before the onset of ICH. Twelve (60%) participants were males with a mean age of 54.25±18.79 years while females were 8 (40%) participants with a mean age of 54.38±10.51 years; with no significant difference, P=0.7. Table 1.

**Table 1: Mean age of participants according to their sex.**

| Sex | | | | P* value |
|---|---|---|---|---|
| Male (n=12, 60% ) | | Female (n=8, 40%) | | |
| Mean age/ years | SD | Mean age/ years | SD | |
| 54.25 | 18.79 | 54.38 | 10.51 | 0.7 |

**Mann Whitney test*

Out of the total; there were 8 (40.0%) patients aged 50 years or less and 12 (60.0%) patients were older than 50 years. Six (30.0%) patients were hypertensive, 2 (10.0%) were diabetics, and 2 (10.0%) were hypertensive and diabetics. Ten (50.0%) patients were smokers.
There was a duration of ≤15 days between the start of COVID-19 infection and the onset of ICH. among 13 (65.0%) patients and 16-30 days among 7 (35.0%) patients. The severity of COVID-19 was mild among 15 (75.0%) patients, moderate among 3 (15.0%), and severe among 2 (10.0%) patients.
Location of hematoma was left deep-seated among 5 (25.0%) patients, right deep-seated among 5 (25.0%), left deep-seated and IVH among 3 (15.0%), right cerebellar among 2 (10.0%), right lobar among only one patient (5.0%), left lobar among 2 (10.0%), Brainstem among only one patient (5.0%), and SAH among only one patient (5.0%) as shown in figure (2).
IgM was positive among 17 (85.0%) patients, IgG was positive among 14 (70.0%), and PCR was positive among 14 (70.0%) patients. Table 2, Figure 1.
The mean SBP among patients was 151.00±20.24 mmHg while the mean DBP among patients was 90.50±6.86 mmHg. Mean levels of Hg were 13.85±2.02 mg/dl, WBC was 11.60±3.60 $10^9$/L, lymphocyte was 16.84±7.95 $10^9$/L, neutrophil was 77.10±14.20 $10^9$/L, platelets were 256.65±71.78 $10^9$/L, CRP was 27.05±28.61 mg/L, D-dimer was 1208.95±948.49 ng/ml, and ferritin was 435.75±237.94 ng/ml. Table 3

**Table 2: Demographic, clinical, and imaging characteristic features of patients, n=20.**

| Characteristic features | | No. | % |
|---|---|---|---|
| Age group | ≤50 years | 8 | 40.0% |
| | >50 years | 12 | 60.0% |
| Risk factor | None | 10 | 50.0% |
| | HT | 6 | 30.0% |
| | DM | 2 | 10.0% |
| | HT+DM | 2 | 10.0% |
| Smoking | Yes | 10 | 50.0% |
| | No | 10 | 50.0% |
| Duration* | ≤15 days | 13 | 65.0% |
| | 16-30 days | 7 | 35.0% |
| Severity | Mild | 15 | 75.0% |
| | Moderate | 3 | 15.0% |
| | Severe | 2 | 10.0% |
| Location of hematoma | Rt deep-seated | 4 | 20.0% |
| | Lt deep-seated | 6 | 30.0% |
| | Lt deep-seated +IVH | 3 | 15.0% |
| | Rt cerebellar | 2 | 10.0% |
| | Rt lobar | 1 | 5.0% |
| | Lt lobar | 2 | 10.0% |
| | Brainstem | 1 | 5.0% |
| | SAH | 1 | 5.0% |
| Positive IgM | | 17 | 85.0% |
| Positive IgG | | 14 | 70.0% |
| Positive PCR | | 14 | 70.0% |
| Total | | 20 | 100.0% |

**The time between the duration of COVID-19 infection and the onset of ICH/days*

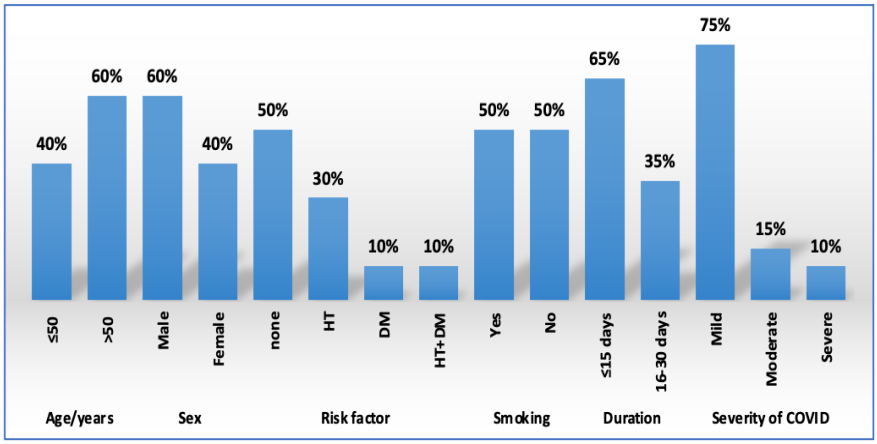


**Figure 1: Demographic and clinical characteristic features of patients, n=20.**

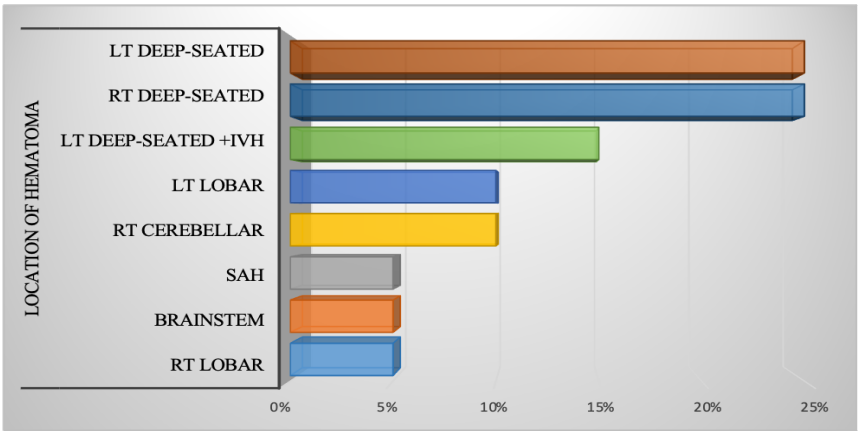


**Figure 2: Location of hematoma among patients, n=20.**

**Table 3: Blood pressure and laboratory data of patients, n=20.**

| Variables | Mean | Standard Deviation |
|---|---|---|
| SBP mmHg | 151.00 | 20.24 |
| DBP mmHg | 90.50 | 6.86 |
| Hb mg/dl | 13.85 | 2.02 |
| WBC count $10^9$/L | 11.60 | 3.60 |
| Lymphocyte % | 16.84 | 7.95 |
| Neutrophil % | 77.10 | 14.20 |
| Platelets $10^9$/L | 256.65 | 71.78 |
| CRP mg/L | 27.05 | 28.61 |
| D-dimer ng/ml | 1208.95 | 948.49 |
| Ferritin ng/ml | 435.75 | 237.94 |

## DISCUSSION:

Numerous neurological symptoms and cerebrovascular disease have been frequently linked to acute SARS-CoV2 infection, given the dilemma between hemorrhagic and thromboembolic complications. However, it is still unclear whether COVID-19 infection and ICH are causally or incidentally related.

Male sex is a known risk factor for ICH [17,18], and the majority of patients in this series were male (60%) as reported in published series where male patients made up 60–80% of the research population. Many researches reveal higher percentages of ICH in female patients with COVID-19, despite the fact that studies show a majority of males over females with ICH [19, 20].

The mean age of presentation for males and females in the current study was 54.3 and 54.4%, respectively, which is significantly younger than predicted; mean patient ages at presentation in many prospective cohort studies and meta-analyses on ICH range from 68 to ≥75 years (21). With COVID-19, this is not the case, though. Similar to this work, Benger et al. [22] reported a mean age of 52.2 years in their COVID-19 and ICH series. In a comparable manner, the mean age recorded in a different series published by Nawabi et al. [18] was 49.5 years; in a different series, Rothstein et al. [23] reported a mean of 57 years, and Aggarwal et al. [24], a mean of 55 years. Many ICH cases linked to COVID-19 infection were seen in individuals who were in their thirties [25,26,27].

Diabetes mellitus and hypertension were the two comorbidities that were most common in this case group. Systemic hypertension and diabetes were shown to be among the most prevalent comorbidities of COVID-19 exacerbated by ICH, according to prior publications [28]. Out of all the patients in the current study, 10 (or 50%) had preexisting hypertension and/or diabetes at the time of presentation, and their systolic and diastolic blood pressure was high. In line with a

narrative review of 36 papers looking at ICH in COVID-19 clinical presentations, it was discovered that 52% of patients had a history of arterial hypertension [29] while another study found that 55.6% of patients had HTN [18].

The CNS may be infected with SARS-CoV-2 either hematogenous or retrogradely through neurons [30]. The cerebral cortex, hypothalamus, and brainstem contain the angiotensin-converting enzyme 2 (ACE2) receptor, which has been suggested as a potential key cellular mediator of COVID-19 invasion [31]. Angiotensin-converting enzyme 2 has been found to play a critical role in the penetration of COVID-19 into body cells. This process allows the virus to enter the cell and causes dysfunction of the "renin-angiotensin-aldosterone system" which in turn damages the lungs and other organs and systems. The local Angiotensin II levels that result from this decrease in ACE2 expression can raise blood pressure and cause endothelial dysfunction in the cerebral arteries, which raises the risk of intracerebral hemorrhage. For this reason, a number of ideas concurred that COVID-19 might make pre-existing hypertension worse, raising the patient's risk of ICH [32, 33].

That is why many theories agreed that COVID-19 may exacerbate preexisted hypertension leading to an increase in the risk of ICH in those patients [32,33].

In this study, four (20%) out of the total number of patients had a history of DM, a finding that was lower than 36.4% out of 33 patients reported by Melmed et al.[34] and 23 (47.9%) out of 48 patients reported by Leasure et al. [35]. According to preclinical research, hyperglycemia accelerates the blood-brain barrier's disintegration, which causes neuronal cell death and brain edoema [36]. Furthermore, it is conceivable that hyperglycemia may act as a mediator in the secondary damage caused by perihematomal edoema, which is linked to a bad prognosis for ICH [37,38]. Human hyperglycemia causes the release of pro-inflammatory cytokines, which last until the patient's blood sugar levels return to normal [39]. Additionally, there is proof that the perihematomal glucose metabolism in human ICH increases gradually and peaks on day three, most likely as a result of an increase in the perihematomal inflammatory cell infiltration [40]. Thus, it is plausible that hyperglycemia increases the inflammatory environment in the brain and oxidative stress, resulting in cellular damage and consequent impairment of secondary neurons [41].

Previous studies in the field of epidemiology and clinical research have definitively shown that: (1) smoking and tobacco use significantly increases the risk of infection-related headaches (ICH) [42], (2) smokers with ICH patients have poorer outcomes and are more likely to die in hospital, (3) current smokers are more likely to experience hematoma expansion (44), and (5) there is a correlation between daily cigarette smoking and intracerebral hemorrhagic volumes in ICH [45].

Due to a variety of factors, such as a transient rise in blood pressure, an impaired blood-brain barrier, increased formation of reactive oxygen species, and activated pro-inflammatory pathways, users of nicotine and tobacco products are more likely to develop spontaneous ICH and worse outcomes following ICH [46].The case series study of five patients by Benger et al. also, reported that the maximum duration between initial infection and presentation of ICH was 30 days in both males and females, ranging between 5 and 30 days. This study also found that there was a delay between the time of COVID-19 symptom onset and the time of ICH diagnosis, with a median of 32 days (range 14 – 38 days). All five of the patients had evidence of prolonged state of inflammation [22].

Surprisingly, the majority of patients in this study 75% had a mild form of Covid-19 infection before developing ICH, while only 10% and 15% of patients had moderate and severe course, respectively. According to a research on COVID-19 patients, out of 19 ICH patients, fifty percent had mild-to-moderate disease, 21 percent had severe disease, and 29 percent had critical disease that required intubation [47]. However, the mechanism of covid-19 in ICH is still not well understood, and this virus with different types of strains that may cause brain damage and/or hemorrhage on different levels of infection severity.

Regarding the site of involvement, 55% of patients in the current study presented deep-seated hemorrhage on CT scan imaging. While Siegler et al. found that 20 (0.14%) patients from 14.483 had ICH with a majority of hemorrhage involvement in the supratentorial site [48]. Additionally, Margos et al. noted in their narrative study that only 7 (3.23%) out of 217 instances had the location of ICH determined in deep structures/basal ganglia, despite the fact that 52% of their patients had hypertension. They get to the conclusion that the uncertain etiopathogenetic cause of arterial hypertension [49]. In a systematic review, deep-seated hemorrhages (in the basal ganglia) were present in only 5.4% of patients [50]. However, this controversy with other reports regarding the high percent of deep-seated hemorrhages may be

because these sites are thought to be susceptible to SARS-CoV-2's selectivity for vascular invasion or compromise., in addition to the associated comorbid systemic hypertension. Thus, the impact of COVID-19 just increases the preexistence risk such as HTN and DM and the ICH cannot be attributed solely to COVID-19 itself.

The majority of patients in the present series had positive PCR on presentation with variable IgM and IgG results, but almost all of them had abnormal D-dimer, CRP, and S. ferritin. Elevated D-dimer and CRP levels are highly suggestive of a hypercoagulability state, however, they do not establish causality between cardiovascular events and COVID-19, and this is in line with a case series study by Reddy et al. of intracranial hemorrhage of PCR positive COVID-19 patients including four patients had elevated D-dimer, CRP, S. ferritin and IgM on admission. D-dimer levels in the early stages of COVID-19 severe respiratory distress may represent acute thrombosis as well as a systemic inflammatory response, according to Zhang et al. Monitoring these levels in conjunction with fibrinogen levels may be helpful for the prompt identification of a thrombotic complication [51,52].

According to a lab investigation of blood indices in this series, almost all of the patients had normal Hb levels, platelets, and abnormal neutrophil, and lymphocyte counts. This is comparable to Abbas et al in their case series study which revealed variable results of blood workup when investigating ICH patients after COVID infection, ranging between normal Hb level to high N/L ratio [47].

These results in addition to D-dimer and CRP in the current case series can be explained as critically ill COVID-19 patients, with a prolonged period between initial infection and the development of ICH [53].

The above-mentioned finding raises many questions, mainly whether COVID-19- causes intracerebral hemorrhage through its pathological process or whether the two conditions coincide. That is why future studies are required to complete the clinical picture of ICH in COVID-19 infection as our case series had showed a unique clinical presentation of COVID-19-associated ICH.

4.1 Limitation of the study:

Our study aimed to scope some light on a potential association between COVID-19 and ICH. However, it had some limitations. First, it is a retrospective case series, of a small sample size. Thus, a causal association between ICH and COVID-19 cannot be determined by the interpretation of the results. A larger sample size in a prospective study design improves the generalizability of our results and may establish causality. second, the outcome of ICH may add some hints to the clinical picture but they were beyond the scope of this study.

## CONCLUSION:

This study provides evidence of ICH in the middle-aged patients demographic, a deep-seated predominance, and a marked systemic inflammatory prodrome. SARS-Covid-19 increases the preexistence risk such as HTN, DM, and the ICH cannot be attributed solely to COVID-19 itself.

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