Spontaneous Intraparenchymal Hemorrhage in Patients with COVID-19: A Prospective Study and Literature Review

Hannan Ebrahimi1 Hadi Digaleh1 Ahmad Pour-Rashidi1, Vahid Kazemi1 Azar Hadadi2 Shahin Nasseri1 Farshid Mirzaii1 Abolghasem Mortazavi1 Abbas Amirjamshidi1,2

1Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran
2Department of Infectious Disease, Sina Hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran

Address for correspondence Ahmad Pourrashidi, MD, Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences, Emam Ave. 1136746911 Tehran, Iran (e-mail: ahmadpourrashidi89@gmail.com).

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Abstract

Introduction  Coronavirus disease 2019 (COVID-19) is a devastating pandemic that may also affect the nervous system. One of its neurological manifestations is intracerebral hemorrhage (ICH). Data about pure spontaneous intraparenchymal hemorrhage related to COVID-19 is scarce. In this study, we present some patients with COVID-19 disease who also had spontaneous intraparenchymal hemorrhage along with a review of the literature.

Methods  This single-center prospective study was done among 2,862 patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) between March 1 and November 1, 2020. Out of 2,862 patients with SARS-CoV-2, 14 patients with neurological manifestations were assessed with a noncontrast brain computed tomography scan. Seven patients with spontaneous intraparenchymal hemorrhage were enrolled.

Results  All seven patients were male, with a mean age of 60.8 years old. Six patients (85.7%) only had minimal symptoms of COVID-19 without significant respiratory distress. The level of consciousness in two patients (28.5%) was less than eight, according to the Glasgow Coma Scale (GCS). Hypertension (71.4%) was the most common risk factor in their past medical history. The mean volume of hematoma was 41cc. Four patients died during hospitalization, and the others were discharged with a mean hospital stay of 42.6 days. All patients with GCS less than 11 died.

Conclusion  It concluded that ICH patients with COVID-19 are related to higher blood volume, cortical and subcortical location of hemorrhage, higher fatality rate, and younger age that is different to spontaneous ICH in general population. We recommend more specific neuroimaging in patients with COVID 19 such as brain magnetic resonance imaging concomitant with vascular studies in future. The impact of COVID-19 on mortality rate is not clear because of limited epidemiologic studies, but identifying the causal relationship between COVID-19 and ICH requires further clinical and laboratory studies.
Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic infection affecting more than 55 million people worldwide. The World Health Organization (WHO) as a global health emergency declares COVID-19 in January 2020.1-3 The burden of disease continues to increase, causing a significant impact on healthcare and the economy worldwide.4 At first, it was thought that COVID-19 only could lead to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or respiratory failure with a high risk of death.5 However, some evidence indicates the cardiovascular, gastrointestinal, urinary, reproductive, and nervous systems impairment.1 Neurological manifestations were considered to be relatively rare.4 The incidence of cerebrovascular disease among SARS-CoV-2 patients admitted to the hospital is estimated at ~2%.6 One of its neurological manifestations is intracerebral hemorrhage (ICH), a devastating complication of COVID-19 associated with significant mortality.7 Although there are some publications about ICH with COVID 19 in the literature, data about pure spontaneous intraparenchymal hemorrhage related to COVID 19 is scarce. In this study, we present some patients with COVID-19 disease who also had spontaneous intraparenchymal hemorrhage along with a review of the literature.

Materials and Methods

In this single-center prospective study, patients with intraparenchymal hemorrhage concomitant with SARS-CoV-2 were collected between March 1 and November 1, 2020, in a tertiary hospital (Sina Hospital), Tehran, Iran. Demographic characteristics of the patients, history, temperature, leucocyte, lymphocyte, hemoglobin, platelets, blood urea nitrogen/creatinine, C-reactive protein (CRP), sodium, liver function tests, D-dimer, lactate dehydrogenase (LDH), coagulation tests, and imaging (chest computed tomography [CT] findings) and real-time polymerase chain reaction (RT-PCR) test results at the time of admission, treatment, length of intensive care unit stay, duration of hospitalization, and outcomes were recorded. Patients aged 18 years and over with spontaneous intraparenchymal bleeding were included in this study. Patients with traumatic intracranial bleeding and patients with any intracranial bleeding except intraparenchymal hemorrhage were excluded. Out of 14 patients, we had 7 patients (comprising some female patients) who were diagnosed intracranial hemorrhage without intraparenchymal component. So, we excluded them to reach homogenous population. The diagram of summarizing the selection of eligible patients is shown in ►Fig. 1.

All patients with neurological manifestations were assessed with a noncontrast brain CT scan with axial 4.8 mm section thickness. The SARS-CoV-2 was established by noncontrast chest CT scan and laboratory virus nucleic acid testing (RT-PCR assay with throat swab samples) at the time of admission under the supervision of an infectious specialist (AH).

Results

In the study period, 2,862 patients with SARS-CoV-2 were identified. Out of 2,862, intracranial hemorrhage was found in 14 patients. Seven cases were excluded after the imaging review because their hemorrhagic sites were out of the cerebral parenchyma. Finally, seven patients with spontaneous intraparenchymal hemorrhage were enrolled (►Fig. 1).

All seven patients were male with a mean age of 60.8 ± 19.9 years old (range: 39–90). The characteristics of patients are shown in ►Table 1. Six patients (85.7%) only had minimal symptoms of COVID-19 without significant respiratory distress. Only second patient was diagnosed with COVID-19 1 week before admission in his quarantine days at home. The other six patients were evaluated on admission time and were identified as COVID-19.

The presentation of all patients was hemiparesis except one who had cerebellar hematoma as clarified in ►Table 1. Two patients (28.5%) were found to have a level of consciousness less than eight, according to GCS (Glasgow Coma Scale). Five patients (71.4%) had a history of acetylsalicylic acid or warfarin consumption. Although all patients had a significant risk factor for intracranial hemorrhage, hypertension (71.4%) was the most common risk factor in their past medical history. The coagulation state was disrupted in two
Table 1  The characteristics of SARS-CoV-2 patients with intraparenchymal hemorrhage

<table>
<thead>
<tr>
<th>Case</th>
<th>History</th>
<th>Presenting COVID-19 symptoms</th>
<th>O₂ saturation (%)</th>
<th>On admission GCS</th>
<th>Seizure</th>
<th>FND</th>
<th>Temperature</th>
<th>Imaging</th>
<th>Laboratory</th>
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**History**

- **Age**: 52, 43, 56, 86, 39, 60, 90
- **Gender**: Male, Male, Male, Male, Male, Male, Male
- **Medical history**: Hypertension, AML, Hypertension diabetes mellitus, Ischemic heart disease, Hypertension Dementia, Psychological disorder, Hypertension Congestive heart failure
- **Relevant medications**: ASA, ASA, atorvastatin, Losartan, Furosemide, Memantine, donepezil, Warfarin, Negative, ASA
- **Presenting COVID-19 symptoms**: Mild, Moderate, Mild, Mild, Mild, Mild, Mild
- **O₂ saturation (%):** 96, 85, 96, 97, 98, 98, 97
- **On admission GCS**: 10, 7, 14, 8, 3, 14, 11
- **Seizure**: Negative, Negative, Negative, Negative, Positive, Negative, Negative
- **FND**: Right hemiparesis, Dysarthria, Left hemiparesis, hemi facial paresis, Left hemiparesis, Left hemiparesis, Left hemiparesis
- **Temperature**: 37, 37.9, 37.2, 37.6, 37.7, 37.3, 37

**Imaging**

- **Volume of hemorrhage (cc)**: 38, 42, 30, 41, 54, 15, 15
- **Location of hemorrhage**: Left thalamus, Right frontoparietal, Right frontoparietal, Right parieto-occipital, Right thalamus, Right thalamus, Cerebellum
- **IVH**: Yes, No, No, No, No, Yes, No

**Laboratory**

- **WBC (per mm³)**: 7,600, 17,500, 9,500, 15,500, 17,600, 12,800, 9,100
- **Lymphocyte (%)**: 38, 12, 18, 16, 19, 7, 16.7
- **Hemoglobin (per mm³)**: 17, 13.4, 13.6, 14.2, 10.6, 14.7, 16.5
- **Platelet (per mm³)**: 205, 16, 206, 133, 276, 288, 94
- **PT (s)**: 14, 17, 65, 16, 60, 13, 15
- **PTT (s)**: 29, 55, 46, 29, 73, 27, 26
- **INR**: 1.07, 1.35, 4.85, 1.23, 6, 1.03, 1.12
- **Creatinine**: 1.1, 1.2, 1.8, 1, 1, 0.5, 0.7
- **BUN**: 14, 49, 47, 41, 34, 16, 21
- **CRP**: 4, 28, 4, 136, 202, 4, 9
- **ESR**: 8, 35, 11, 24, 9, 7, 11
- **Na**: 135, 139, 137, 134, 142, 139, 139
- **D-dimer**: 227, 1252, 427, 735, 958, 600, 650
- **AST**: 71, 62, 30, 60, 48, 49, 69
- **ALT**: 69, 69, 26, 50, 36, 28, 33
- **ALP**: 161, 171, 146, 166, 238, 239, 146
- **LDH**: 428, 1285, 357, 721, 780, 427, 344

(continued)
patients (28.5%). A high level of CRP, erythrocyte sedimentation rate (ESR), LDH, and D-dimer were detected in three patients (42.8%).

The mean volume of hematoma was 41 cc (range: 30–54 cc; ►Fig. 2). Intraventricular hematoma was seen in two patients (28.5%). Except fourth patient (who died before initiation of the operation) and sixth patient (who managed conservatively), decompressive craniectomy and evacuation of hematoma were done in the other five. Also, in first patient, external ventricular catheter was inserted. Four patients died during hospitalization, and the others were discharged with a mean hospital stay of 42.6 days. All patients with GCS less than eleven died.

**Table 1** The characteristics of SARS-CoV-2 patients with intraparenchymal hemorrhage

<table>
<thead>
<tr>
<th>Case</th>
<th>History</th>
<th>Treatment and outcome</th>
<th>Hospital stay (d)</th>
<th>Intervention</th>
<th>Outcome</th>
<th>mRS</th>
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<tr>
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<td>59</td>
<td>Surgery</td>
<td>1</td>
<td>Surgery</td>
<td>Died</td>
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<td>73</td>
<td>Conservative</td>
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<td>Failed surgery</td>
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<td>124</td>
<td>Surgery</td>
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<td>Surgery</td>
<td>Died</td>
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<tr>
<td>4</td>
<td>15</td>
<td>Conservative</td>
<td>2</td>
<td>Conservativesurgery</td>
<td>Died</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>Surgery</td>
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<td>Surgery</td>
<td>Discharged</td>
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<tr>
<td>6</td>
<td>28</td>
<td>Conservative</td>
<td>0</td>
<td>Surgery</td>
<td>Discharged</td>
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</tbody>
</table>

Abbreviations: BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ASA, acetylsalicylic acid; aPTT, activated partial-thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FND, focal neurological deficit; GCS, Glasgow Coma Scale; INR, international normalized ratio; IVH, intraventricular hemorrhage; LDH, lactate dehydrogenase; mRS, modified Rankin Scale; PT, prothrombin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WBC, white blood cell.

**Fig. 2** Axial brain (A, C, E, G, I, K, and M) and chest computed tomography (B, D, F, H, J, L, and N) scan of the patients showing intracerebral hemorrhage along with the pattern of pulmonary involvement by coronavirus disease 2019 (patient no. 1: A and B; patient no. 2: C and D; patient no. 3: E and F; patient no. 4: G and H; patient no. 5: I and J; patient no. 6: K and L; patient no. 7: M and N).
Discussion

Evidence is increasing from clinical studies in the literature that infection with SARS-CoV-2 can lead to spontaneous intraparenchymal hemorrhage.\(^7\)\(^7\)\(^\text{-}\)\(^18\) However, the relationship or association between ICH and COVID-19 is unclear because of limited documents on this topic. Our literature review about publications with more than one COVID-19 patient concomitant with intraparenchymal hematoma is shown in Table 2.\(^7\)\(^\text{-}\)\(^18\) Most of the publications are heterogeneous, and patients with traumatic hematoma were included. In this study, we report only patients with COVID-19 and spontaneous intraparenchymal hemorrhage. In agreement with the other publications, our study showed that most of the patients were younger than 60 years old male. It means COVID-19-related intraparenchymal hemorrhage may occur in a younger age range relative to spontaneous ICH.

Pathophysiology underlying ICH in patients with COVID-19 is challenging to establish and may be variable.\(^10\) The literature revealed some hypothesis about this coexistence, including evidence of the neuroinvasive potential of coronavirus, endothelitis, vasculitis, thrombocytopenia, disseminated intravascular coagulation, platelet dysfunction, consumptive coagulopathy, microbleeding, and microvascular thrombosis, neurotropism toward angiotensinogen-converting enzyme type 2 receptors, autoimmunity and cytokine storm, and hypercoagulable state.\(^11\)\(^,\)\(^12\) Also, endothelial damage due to hypoxia and inflammatory milieu has been shown to occur in SARS-CoV-2, and microscopic disruption of the endothelium of cerebral veins could lead to microbleedings and eventual ICH.\(^7\)\(^,\)\(^18\) Identification of the causal relationship between COVID-19 and ICH requires further clinical and laboratory studies. Laboratory studies including pathologic investigations and checking the molecules like matrix-metalloproteinase on tissue samples along with a larger clinical study can help to discover this relationship.

The most important risk factors in spontaneous ICH are chronic arterial hypertension, cerebrovascular amyloid deposition; coagulopathies (i.e., the use of antithrombotic or thrombolytic agents, congenital or acquired factor deficiencies) and systemic diseases, such as thrombocytopenia; the use of oral anticoagulants, especially vitamin K inhibitors (i.e., warfarin); psychosocial, ethnic, and economic factors (common in low-income and middle-income countries); old age; and an elevated alcohol intake.\(^20\)\(^\text{-}\)\(^23\) In a study conducted by Melmed et al, risk factors for ICH in patients with COVID 19 were assessed. Older age, noncaucasian race, respiratory failure requiring mechanical ventilation, and therapeutic anticoagulation were associated with ICH on univariate analysis.\(^7\) In a report by Kvernland et al, coagulopathy was the most common etiology (73.7%) among patients with COVID-19 and hemorrhagic stroke, and patients with COVID-19 had higher initial international normalized ratio, partial thromboplastin time, and fibrinogen levels.\(^9\) Besides, Melmed et al reported significant coagulation disturbance in COVID-19 patients with ICH compared with COVID-19 patients without ICH.\(^7\) In agreement with the others, hypertension and coagulopathy were some predisposing factors in our study.

Mortality rates for hemorrhagic pathology can vary significantly depending on the type, location, etiology, acuity, and severity. Dogra et al reported a 100% mortality rate in five patients with extensive parenchymal hemorrhages causing mass effect and herniation.\(^8\) In a study by Nawabi

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>No. of patients with parenchymal hemorrhage</th>
<th>Mean age (y)</th>
<th>Gender (male; %)</th>
<th>Coagulopathy (%)</th>
<th>Mortality %</th>
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<tr>
<td>Melmed et al(^7)</td>
<td>37</td>
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<td>78.8</td>
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<td>Altschul et al(^10)</td>
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<td>48.5</td>
<td>50</td>
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<td>Benger et al(^13)</td>
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<td>Hernández-Fernández et al(^14)</td>
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<td>Pavlov et al(^16)</td>
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<td>Ghani et al(^16)</td>
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<td>59</td>
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<td>Carroll and Lewis(^17)</td>
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<td>Morassi et al(^18)</td>
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<td>7</td>
<td>60.8</td>
<td>100</td>
<td>2 (33.3%)</td>
<td>4 (66.6%)</td>
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Abbreviations: COVID-19, coronavirus disease 2019; ND, not defined.
et al, a combination of acute intracranial hemorrhage and COVID-19 led to death in eight patients (44.4%). In our study, 57% of patients, including all patients with GCS less than eleven, died. The impact of COVID-19 on mortality rate is not clear because of limited epidemiologic studies with little sample size.

As a limitation, our small sample size can affect our results, and a widespread multicentric study can be useful in determining COVID-19 effects in patients with ICH. Also, not performing the autopsy was another limitation in our study. We sent some samples for pathology to evaluate them in terms of any evidence related to COVID-19, but unfortunately pathology department reported no specific characteristics differentiating from the other samples accurately.

**Conclusion**

It concluded that ICH patients with COVID-19 are related to higher blood volume, cortical and subcortical location of hemorrhage, higher fatality rate, and younger age that is different to spontaneous ICH in general population. We recommend more specific neuroimaging in patients with COVID-19 such as brain magnetic resonance imaging concomitant with vascular studies in future. The impact of COVID-19 on mortality rate is not clear because of limited epidemiologic studies but identifying the causal relationship between COVID-19 and ICH requires further clinical and laboratory studies.

**Conflict of Interest**

None declared.

**References**