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

Hannan Ebrahimi[1] Hadi Digaleh[1] Ahmad Pour-Rashidi[1,] Vahid Kazemi[1] Azar Hadadi[2] Shahin Nasseri[1] Farshid Mirzaii[1] Abolghasem Mortazavi[1] Abbas Amirjamshidi[1,]

[1]Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[2]Department 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).

Indian J Neurosurg 2022;11:210–215

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.

Keywords
- coronavirus
- COVID-19
- intracerebral hemorrhage
- spontaneous intraparenchymal hemorrhage

DOI https://doi.org/10.1055/s-0041-1735352
ISSN 2277-954X

Thieme Medical and Scientific Publishers Pvt. Ltd. A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

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).

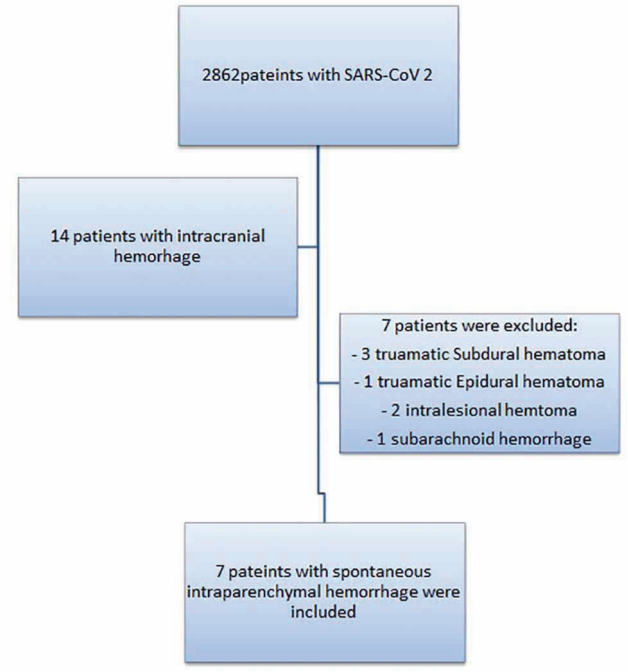

Fig. 1 Flowchart summarizing the selection of eligible patients. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

The Ethics Committee of Sina Hospital, Tehran University of Medical Sciences, approved this study. Statistical analysis was performed with SPSS (version 18, IBM, Armonk, New York, United States). Descriptive statistics were mean and standard deviation for the quantitative variables and frequencies for qualitative variables.

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

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
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	Hypertension Congestive heart failure
Relevant medications	ASA	ASA atorvastatin	Warfarin Losartan Furosemide	Memantine donepezil	Warfarin	Negative	ASA
Presenting COVID-19 symptoms	Mild	Moderate	Mild	Mild	Mild	Mild	Mild
O_2 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 hemip-aresis, hemi facial paresis	Left hemiparesis	Left hemiparesis	Left hemiparesis	Left hemiparesis	Negative
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 parie-to-occipital	Right thalamus	Right thalamus	Cerebellum
IVH	Yes	No	No	No	No	Yes	No
Laboratory							
WBC (per mm^3)	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 mm^3)	17	13.4	13.6	14.2	10.6	14.7	16.5
Platelet (per mm^3)	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)

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

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
History							
Treatment and outcome							
Hospital stay (d)	59	1	73	124	15	27	28
Intervention	Surgery	Conservative	Surgery	Failed surgery	Surgery	Conservative	Surgery
Outcome	Died	Died	Discharged	Died	Died	Discharged	Discharged
mRS	–	–	2	–	–	0	3

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.

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.

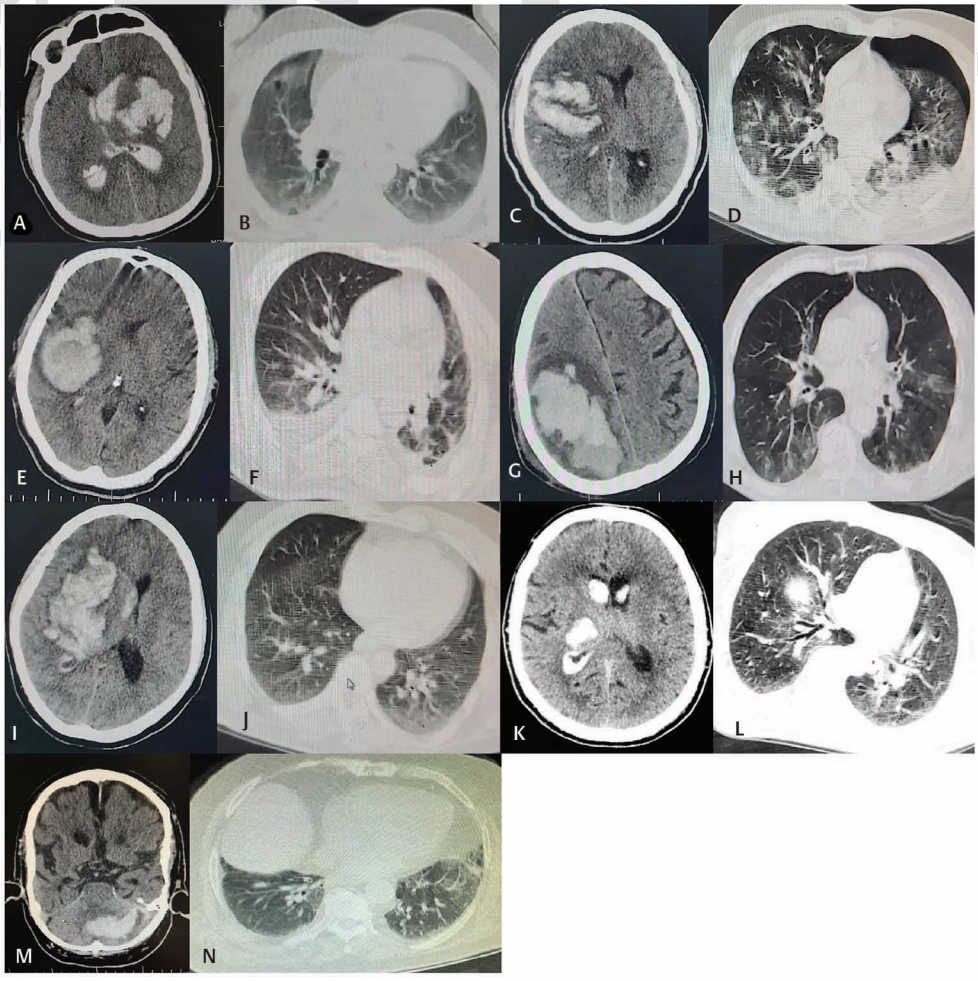

Fig. 2 Axial brain (**A**, **C**, **E**, **G**, **I**, **K**, and **M**) and chest computed tomography (**B**, **D**, **F**, **H**, **J**, **L**, and **N**) scan of the patients showing intracerebral hemorrhage along with the pattern of pulmonary involvement by coronavirus disease 2019 (patient no. 1: **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.[7-18] 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** [7-18] 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.[7,19] 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.[20-23] 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 ration, 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 2 All publications with more than one COVID-19 patient concomitant with intraparenchymal hematoma

Author	No. of patients	No. of patients with parenchymal hemorrhage	Mean age (y)	Gender (male; %)	Coagulopathy (%)	Mortality %
Melmed et al[7]	37	33	61.6	78.9	ND	51.5
Dogra et al[8]	33	33	61.6	78.8	ND	33%
Kvernland et al[9]	34	19	60	78.9	14 (73.7%)	84.2
Altschul et al[10]	35	16	56	62.5	7 (43.7%)	40
Nawabi et al[11]	18	6	48.5	50	ND	44.4
Mousa-Ibrahim et al[12]	6	6	68.5	50	1 (16.6%)	50
Benger et al[13]	5	5	52.2	60	3 (60%)	0
Hernández-Fernández et al[14]	5	5	62.6	80	ND	40
Fayed et al[15]	3	3	60.7	33.3	0	33%
Pavlov et al[5]	3	3	58	100	0	0
Ghani et al[16]	3	2	59	50	2 (66.6%)	100
Carroll and Lewis[17]	2	2	68	100	0	100
Morassi et al[18]	6	2	57	100	1 (50%)	100
Present study	7	7	60.8	100	2 (33.3%)	4 (66.6%)

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%).[11] 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

1 Fatehi P, Hesam-Shariati N, Abouzaripour M, Fathi F, Hesam Shariati MB. Acute ischemic and hemorrhagic stroke and COVID-19: case series. SN Compr Clin Med 2020 (e-pub ahead of print). DOI: 10.1007/s42399-020-00559-8

2 Poggiali E, Bastoni D, Ioannilli E, Vercelli A, Magnacavallo A. Deep vein thrombosis and pulmonary embolism: two complications of COVID-19 pneumonia? Eur J Case Rep Intern Med 2020;7(5):001646

3 Coronavirus disease (COVID-19) pandemic. (2020). Accessed June 24, 2021 at https://www.who.int/emergencies/diseases/novel-coronavirus-2019

4 Gogia B, Fang X, Rai P. Intracranial hemorrhage in a patient with COVID-19: possible explanations and considerations. Cureus 2020;12(8):e10159

5 Pavlov V, Beylerli O, Gareev I, Torres Solis LF, Solís Herrera A, Aliev G. COVID-19-related intracerebral hemorrhage. Front Aging Neurosci 2020;12:600172

6 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–690

7 Melmed KR, Cao M, Dogra S, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. J Thromb Thrombolysis 2021;51(4):953–960

8 Dogra S, Jain R, Cao M, et al. Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis 2020;29(8):104984

9 Kvernland A, Kumar A, Yaghi S, et al. Anticoagulation use and hemorrhagic stroke in SARS-CoV-2 patients treated at a New York Healthcare System. Neurocrit Care 2021;34(3):748–759

10 Altschul DJ, Unda SR, de La Garza Ramos R, et al. Hemorrhagic presentations of COVID-19: risk factors for mortality. Clin Neurol Neurosurg 2020;198:106112

11 Nawabi J, Morotti A, Wildgruber M, et al. Clinical and imaging characteristics in patients with SARS-CoV-2 infection and acute intracranial hemorrhage. J Clin Med 2020;9(8):2543

12 Mousa-Ibrahim F, Berg S, Od TPDetola O, Teitcher M, Ruland S. Intracranial hemorrhage in hospitalized SARS-CoV-2 patients: a case series. J Stroke Cerebrovasc Dis 2021;30(1):105428

13 Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: clinical characteristics from a case series. Brain Behav Immun 2020;88:940–944

14 Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain 2020;143(10):3089–3103

15 Fayed I, Pivazyan G, Conte AG, Chang J, Mai JC. Intracranial hemorrhage in critically ill patients hospitalized for COVID-19. J Clin Neurosci 2020;81:192–195

16 Ghani MU, Kumar M, Ghani U, Sonia F, Abbas SA. Intracranial hemorrhage complicating anticoagulant prophylactic therapy in three hospitalized COVID-19 patients. J Neurovirol 2020;26(4):602–604

17 Carroll E, Lewis A. Catastrophic intracranial hemorrhage in two critically ill patients with COVID-19. Neurocrit Care 2021;34(1):354–358

18 Morassi M, Bagatto D, Cobelli M, et al. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol 2020;267(8):2185–2192

19 Sweid A, Hammoud B, Bekelis K, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke 2020;15(7):733–742

20 de Oliveira Manoel AL, Goffi A, Zampieri FG, et al. The critical care management of spontaneous intracranial hemorrhage: a contemporary review. Crit Care 2016;20:27210.1186/s13054-016-1432-0

21 Zheng H, Chen C, Zhang J, Hu Z. Mechanism and therapy of brain edema after intracerebral hemorrhage. Cerebrovasc Dis 2016;42(3-4):155–169

22 Howard G, Cushman M, Howard VJ, et al. Risk factors for intracerebral hemorrhage: the REasons for geographic and racial differences in stroke (REGARDS) study. Stroke 2013;44(5):1282–1287

23 Flaherty ML, Woo D, Haverbusch M, et al. Racial variations in location and risk of intracerebral hemorrhage. Stroke 2005;36(5):934–937

