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Review article

Intracerebral hemorrhage in COVID-19: A narrative review

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ABSTRACT

Coronavirus Disease 19 (COVID-19) pandemic affects the worldwide healthcare system and our understanding of this disease grows rapidly. Although COVID-19 is a mainly respiratory disease, neurological manifestations are not uncommon. The aim of this review is to report on the etiology, clinical profile, location, and outcome of patients with intracerebral hemorrhage (ICH) and COVID-19. This review includes 36 studies examining ICH in the clinical presentation of COVID-19. Overall, 217 cases with intracranial hemorrhage, of which 188 ICHs, were reported. Generally, a low incidence of both primary and secondary ICH was found in 8 studies [106 (0.25%) out of 43,137 hospitalized patients with COVID-19]. Available data showed a median age of 58 years (range: 52–68) and male sex 64%, regarding 36 and 102 patients respectively. Furthermore, 75% of the patients were on prior anticoagulation treatment, 52% had a history of arterial hypertension, and 61% were admitted in intensive care unit. Location of ICH in deep structures/basal ganglia was ascertained in only 7 cases making arterial hypertension an improbable etiopathogenetic mechanism. Mortality was calculated at 52.7%. Disease related pathophysiologic mechanisms support the hypothesis that SARS-CoV2 can cause ICH, however typical ICH risk factors such as anticoagulation treatment, or admission to ICU should also be considered as probable causes. Physicians should strongly suspect the possibility of ICH in individuals with severe COVID-19 admitted to ICU and treated with anticoagulants. It is not clear whether ICH is related directly to COVID-19 or reflects expected comorbidity and/or complications observed in severely ill patients.

1. Introduction

1.1. Pathophysiology and transmission of COVID-19

Coronavirus disease (COVID-19) has become the most difficult challenge for modern medicine, as it has manifested into a worldwide pandemic by infecting over 61 million people as of November 24, 2020. The etiological factor is coronavirus 2 (SARS-CoV2), which infects the host cells by binding through the surface spike protein (mediated by transmembrane serine protease 2) to the human angiotensin converting receptor (ACE 2) [1–3].

SARS-CoV2 entry in cells causes cellular injury and finally cellular death. Subsequently, the formation of damage associated molecular patterns (DAMP's) extracellularly and pathogen associated molecular patterns (PAMP's) intracellularly leads to DAMP and PAMP recognition by pattern recognition receptors on endothelial cells and alveolar macrophages, thus triggering the induction of proinflammatory cytokine transcription factors [4]. This leads to a pulmonary recruitment of macrophages and dendritic cells which phagocytose SARS-CoV2 and migrate to secondary lymphoid organs further propagating cytokine release. Increased cytokine levels are associated with more severe disease [5].

Transmission of SARS-CoV2 occurs through both direct or indirect means. Human to human transmission via inhalation of mucosalivary droplets which can remain intact, contagious and airborne for at least 3 h is considered the direct mechanism of transmission [6]. Contact with contaminated objects and then with mucous membranes can indirectly transmit the disease. SARS-CoV2 can also be transmitted from asymptomatic carriers without any radiological finding or patients who are in the incubation period [7].

1.2. Clinical characteristics of COVID-19

COVID-19 disease is characterized by a variety of clinical manifestations ranging from asymptomatic state to Acute Respiratory Distress Syndrome (ARDS) and multiorgan failure, but primary involves the respiratory system. Initial symptoms typically include

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fever, dry cough, sore throat, headache, fatigue, myalgia and shortness of breath [8]. Confusion, diarrhea, nausea and vomiting, rhinorrhea and skin rash, as well as conjunctivitis have also been reported in COVID-19 [7]. Anosmia and dysgeusia are the most common early neurological symptoms of COVID-19 (occurring to up to 80% of patients) [9,10], whilst encephalopathy is common in critically ill patients [11]. Ischemic and hemorrhagic strokes have also been reported and must be taken into consideration when assessing COVID-19 patients with known vascular risk factors [12]. Other neurological manifestations include Guillain-Barré syndrome and its variants, meningoencephalitis, acute disseminated encephalomyelitis, acute hemorrhagic necrotizing encephalopathy [11], generalised myoclonus, ataxia [13], posterior reversible encephalopathy syndrome, and seizures [11].

Abnormal coagulation parameters have also been observed and are associated with poor prognosis [14]. Additionally, SARS-CoV2 can cause liver dysfunction, acute kidney failure, acute myocarditis, heart failure and shock [10]. In patients who demonstrate an extreme rise in cytokines by the end of the first week, the disease can progress to pneumonia, ARDS, multisystem failure, and finally death [4].

1.3. Intracerebral hemorrhage in patients with COVID-19

Intracerebral hemorrhage (ICH) is a very rare but well documented complication of COVID-19. Primary ICH could occur in the absence or presence of known risk factors, such as arterial hypertension (HTN) or anticoagulation therapy (pre-treatment of unrelated disease or COVID-19 thromboprophylaxis). ICH may also be secondary to hemorrhagic transformation of an acute ischemic stroke or to complications of revascularization procedures; cerebral sinus thrombosis can also cause brain hemorrhage. Symptoms are usually focal, depending on the affected cerebral region but can also be non-specific. Patients with ICH typically present with severe headache, hemiparesis, eye deviation and impaired levels of consciousness. Brain imaging such as a rapid computed tomography (CT) is mandatory and must be performed urgently in order to distinguish between ICH and ischemic stroke [15]. CT angiography is a highly specific test and is suitable for bleeding source detection. Other options include brain magnetic resonance imaging and angiography [16]. Treatment usually involves hemodynamic and neurological stabilization, management of the underlying conditions and, in selected cases, neurosurgical intervention [17].

2. Methodology

Pubmed and Google Scholar were used as search tools to identify relevant studies and articles, with the last search being performed on November 20th 2020. Keywords include: "COVID-19", "Intracerebral", "Cerebral" and "Hemorrhage". Inclusion criteria parameters include: All article types written in English language and published in the last year that examine COVID-19 in combination with ICH. Articles excluded from the review were not written in English language and/or did not provide a full-text publication. Our initial search yielded 2365 search results out of which 36 original studies met our inclusion criteria.

The aim of this narrative review is to report on the etiology, clinical profile, location, and outcome of patients with ICH and COVID-19.

3. Results

Thirty-six original studies, case series and reports, reported a total of 217 cases with intracranial hemorrhage, of which 188 were ICHs (Table 1) [2,18–52]. However, in some reports intracranial hemorrhage was used as a broader term co-reporting ICH with other types of brain hemorrhage (subarachnoid hemorrhage (SAH), primary intraventricular, subdural hemorrhage).

3.1. Incidence

Data from 8 studies [18,25] including 43,137 hospitalized patients with COVID-19 reported a total number of 122 (0.28%) cases of intracranial hemorrhage, of which 106 (0.25%) were ICHs. Of the 106 reported ICH cases, 80 (75.5%) were considered primary, whilst the remaining 26 were all secondary to hemorrhagic transformation of ischemic stroke. The remaining 16 cases developed other type of intracranial hemorrhage (8 were SAH and 8 could not be identified).

3.2. Age and sex

Four studies [20,22,23,26] reported 63 hospitalized patients with intracranial hemorrhage with a mean age that ranged from 57 (±7.0) to 69.4 (±9.8) years; a median age that ranged from 49.5 (range: 39.5 – 62.8) to 62 (range: 37 – 83) was reported in 3 studies regarding 70 patients [18,21,27]. A median age of 58 years (range: 52–68) was calculated in 36 cases of ICH regarding 23 studies [2,24,29,31,33–44,46–52].

Male sex was reported in 134 (65%) out of 206 patients with intracranial hemorrhages, [18–23,26,27,29–52] and 65 (64%) out of 102 patients with ICH [2,18,22,26,29,31–52].

3.3. History of arterial hypertension and prior use of anticoagulants

History of arterial HTN was reported in 89 (54%) out of 164 patients with intracranial hemorrhage, [2,18,19,21–24,26,27,30–34,36,41,42,44–47,49,51] and in 45 (52%) out of 87 patients with ICH [2,18,22,24,26,31–34,36,41,42,44–47,49,51].

Anticoagulation prior to onset of brain hemorrhage was administered in 88 (75%) out of the 118 patients with intracranial hemorrhage [2,18,21–23,27,29–31,33–35,39,42–48,49,50], and 54 (75%) of the 72 patients with ICH [2,18,22,29–31,33–35,39,42–48,49,50]. The type of anticoagulation treatment was reported in 67 cases with intracranial hemorrhages; in 62 of them anticoagulation treatment was initiated in-hospital (39 received unfractionated heparin (UFH), 16 low molecular weight heparin (LMWH), 4 heparin & argatroban, 3 heparin switched to LWMH), and 5 have been on long term anticoagulant treatment (3 were receiving warfarin, and 2 warfarin/dabigatran) [2,18,21,29–31,33–35,39,42,44,49,50].

3.4. Intensive care unit admission prior to intracranial hemorrhage

ICU admission prior to brain hemorrhage was reported in 73 (64%) of the 115 patients who subsequently developed intracranial hemorrhage, [2,21–23,26,27,29–35,38–52] and 42 (61%) of the 69 who subsequently developed ICH [2,22,26,29–35,38–52].

3.5. Time from COVID-19 symptoms to diagnosis of hemorrhage

Median time from COVID-19 symptoms to diagnosis of brain hemorrhage ranged from 1 to 32 days amongst 6 reviewed studies [2,18–20,23,27].

3.6. Etiology and location of ICH

Out of 188 ICHs, 149 (79%) were primary, [2,18–28,30–38,41,43–48,50] including those with or without known risk factors such as arterial HTN, prior use of anticoagulants or extracorporeal membrane oxygenation (ECMO); 29 ICHs were secondary to hemor-

Table 1
Reviewed studies and findings (n = 36).[a]

Study	Number of intracranial hemorrhages/total number of cases with COVID-19 (n of ICH)	Sex (male) n	Age in years	History of HTN n	ICU admission prior to hemorrhage	Anticoagulation therapy at the time of ICH n	Hemorrhage location n	Etiology of hemorrhage	Days from COVID-19 to stroke diagnosis Median (range)	Other Findings
Dogra et al. [18]	33/3824 (33 ICH)	26	Median (range): 62 (37 – 83)	16	NR	22 (15 UFH, 3 on UFH + LMWH, 3 UFH + argatroban, 1 enoxaparin) 3 (type of drug NR) + 2 long term (warfarin and dabigatran)	NR	7 Primary ICH, 26 Secondary to HT of ischemic stroke	17 (8–23)	Long-term treatment prior to ICH: 7 on aspirin, 2 aspirin + clopidogrel, 1 on cilostazol, 1 clopidogrel ICH score median: 2 (range: 1–2)Mortality: 42.4% (14/33)
Siegler et al. [19]	28/14,483 (20 ICH)	18	–	18	NR	NR	13 supratentorial ICHs 7 infratentorial ICHs 8 other types of intracranial hemorrhage	Primary ICHs	3,5 (1 – 7)	ICH score median: 3 (range: 1–3) NIHSS score median: 22 (7 – 25)Mortality:16/28 (58,3%)
Shahjouei et al [20]	27 / 17,799 (25 ICH)	19	Mean (SD) 62,5 (15.3)	NR	NR	NR	ICHs NR, 2 SAH	Primary ICHs	1 (0–5)	NIHSS score median: 13 (8 – 17) ICH score median: 3 (2 – 4)
Kvernland et al. [21]	19/4071 (16 ICH)	15	Median (range): 60 (51–63)	8	16	17 (13 heparin, 2 enoxaparin, 2 long-term warfarin)	6 lobar intraparenchymal (IPH) ICHs 4 multifocal cortical, 1 multifocal IPH, 1 subcortical, 2 cortical, 2 cerebellar 3 SAH	Primary ICHs	NR	Mortality: 11/19 (57.9%) at follow-up 15 with HT of ischemic stroke were excluded from this study In 1 patient heparin was changed to argatroban.
Hernández- Fernández et al. [22]	5 ICH/ 1683	4	Mean (SD): 62,6 (7.2)	4	3	3 (type NR)	3 lobar ICHs (1 left frontal,1 left frontal with SAH expansion, 1 left temporal) 1 basal ganglia ICH 1 focal cortico-subcortical ICH with SAH involvement	Primary ICHs	NR	Mortality: 2/5
Rothstein et al. [23]	8/ 844 (5 ICH)	4	Mean (SD)57 (7.0)	6	6	7 (type NR}	5 lobar ICHs 3 SAH	Primary ICHs	25 (17–29)	4/7 treated with anticoagulants on simultaneous antiplatelet drugs 6/8 patients died in-hospital
Li et al. [24]	1 ICH/ 219	NR	60	1	NR	NR	NR	Primary ICHs	10	Died 13 days after ICH
Ling Mao et al. [25]	1 ICH/ 214	NR	NR	NR	NR	NR	NR	Primary ICHs	NR	Cause of death: respiratory failure
Behzandia et al. [26]	23 ICH	11	Mean (SD)69.4 (9.8)	8	8	NR	16 lobar ICHs 7 non-lobar ICHs	Primary ICHs	NR	
Nawabi et al. [27]	18 (6 ICH)	9	Median (range): 49,5 (39.5 –	10	8	8 (type NR)	6 ICHs (4 lobar, 1 deep, 1 infratentorial) 2 primary intraventricular	Primary ICHs	1.5 (0 – 3)	1 case, ICH was diagnosed as a first manifestation of COVID-19. 1 patient on antiplatelets

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Table 1 (*continued*)

Study	Number of intracranial hemorrhages/total number of cases with COVID-19 (n of ICH)	Sex (male) n	Age in years	History of HTN n	ICU admission prior to hemorrhage	Anticoagulation therapy at the time of ICH n	Hemorrhage location n	Etiology of hemorrhage	Days from COVID-19 to stroke diagnosis Median (range)	Other Findings
			62.8)				9 SAH 1 subdural hematoma			
Varathatraj et al. [28]	9 ICH	NR	NR	NR	NR	NR	NR	Primary ICHs	NR	
Argiro et al. [29]	6 ICH	3	Median (range) 64,5 (58.75 – 75)	NR	4	5 - LMWH	6 lobar ICHs (4 parietal, 1 temporal 1 parieto-occipital and temporal)	Secondary to Cerebral Vein Thrombosis	NR	
Benger et al.[2]	5 ICH	3	Median (range) 52 (45,5 – 59)	4	4	5 (2 LMWH, 2 IV heparin, 1 warfarin)	3 lobar ICHs, 1 multi-lobar ICH 1 basal ganglia ICH	Primary ICHs	32 (14–38)	Patients with HTN developed lobar and multilobar ICHs whereas the patient with no history of HTN developed basal ganglia hemorrhage
Usman et al. [30]	4 (3 ICH)	3	Mean (range) 53.7 (50,5–58,25)	2	4	4 (3 UFH, 1 UFH + argatroban)	3 lobar ICHs (1 frontal with SAH expansion, 1 frontal-temporal, 1 temporal with intraventricular expansion) 1 SAH	Primary ICH	5,5 (3 – 18) from ECMO administration	All 4 on ECMO. All 3 patients with ICHs died.
Goncalves et al. [31]	3 ICH	1	56, 40s, 60s	0	3	3 (2 enoxaparin, 1 UFH)	1 cerebellar 1 multifocal (frontal and occipital lobes, thalamus) 1 multifocal (basal ganglia, frontal & occipital lobes)	2 Primary 1 due to cerebral vein thrombosis	15 (15, 16, 15)	Mortality: 3/3
Bihlmaier et al. [32]	3 ICH	2	Medium age (56.6)	2	3	NR	3 multifocal	Primary ICH	NR	3 patients on ECMO and 1 on long-term acetylsalicylic acid. Mortality: 3/3
Fayed et al. [33]	2 ICH	1	57, 71	2	2	1 - heparin, 1 NR	2 lobar ICHs(1 frontal, 1 occipital)	Primary ICHs	20	1/2 patients died, following complications of ICH (cerebral circulatory arrest)
Morassi et al. [34]	2 ICH	2	57 (both cases)	1	2	1 - enoxaparin	2 lobar ICHs (1 Bilateral, 1 Frontal extending to ventricles)	Primary ICHs	14 & 17	One patient only on dual antiplatelet therapy Both died on the same day of ICH diagnosis
Ghani et al. [35]	2 ICH	1	59 (both cases)	NR	2	2 (1 IV UFH and 1 apixaban switched to enoxaparin)	Locations NR (1 with SAH expansion, and 1 intraventricular expansion)	Primary ICHs	NR	
Agarwal et al. [36]	2 ICH	2	56, 72	1	NR	NR	1 pontine with intraventricular expansion 1 multifocal	Primary ICH	0 & NR	Mortality: 1/2
Sharifi-Razavi et al.	1 ICH	Male	79	NR	NR	NR	1 right hemisphere, accompanied by intraventricular and	Primary ICH	3	Patient admitted for ICH and later confirmed COVID-19 infection, though mild symptoms of infection were

Table 1 (*continued*)

Study	Number of intracranial hemorrhages/total number of cases with COVID-19 (n of ICH)	Sex (male) n	Age in years	History of HTN n	ICU admission prior to hemorrhage	Anticoagulation therapy at the time of ICH n	Hemorrhage location n	Etiology of hemorrhage	Days from COVID-19 to stroke diagnosis Median (range)	Other Findings
[37]							subarachnoid hemorrhage			already present
Bao et al. [38]	1 ICH	Male	38	NR	1	NR	Lobar ICH extending to basal ganglia.	Primary ICH	0	The diagnosis of COVID-19 was made 7 days after admission with positive PCR test results; subsequent PCR tests were found negative. No COVID-19 symptoms prior admission
Motoie et al. [39]	1 ICH	male	50	NR	1	1 - IV UFH	Multifocal	Secondary ICH to HT of an ischemic stroke	10	Patient on ECMO. Patient in hypercoagulable state prior to ICH. The patient died 8 days after ICH onset.
Al – Olama et al. [40]	1 ICH	Male	36	NR	0	NR	1 lobar ICH (frontal with subdural extension)	Secondary ICH to COVID-19 encephalitis	6	Radiologically ICH was attributed to viral encephalitis
Kim et al. [41]	1 ICH	Female	53	0	0	NR	1 basal ganglia ICH (external capsule and putamen with intraventricular expansion)	Primary ICH	5	Patient was positive for COVID-19 but was asymptomatic until the development of ICH. 30 days after admission ICH symptoms started improving
Khattar et al. [42]	1 ICH	Male	42	1	1	1 - IV heparin	multi-loculated centered in the lentiform nucleus	Possibly secondary due to HT of ischemic stroke	29	ICH was diagnosed 8 days after IV heparin was first administered due to hypercoagulable state.
Thu et al. [43]	1 ICH	Male	72	NR	1	0	Lobar ICH (olfactory gyrus)	Primary ICH	NR	
Gogia et al. [44]	1 ICH	Male	75	1	1	1 - Enoxaparin/ also on aspirin and clopidogrel	Multifocal	Primary ICH	17 days post admission.	Clinical course was complicated by herniation due to ICH and patient deceased on the same day of ICH diagnosis.
Daci et al. [45]	1 ICH	Female	60s	0	0	0	Bilateral basal ganglia ICH with effacement of lateral ventricules	Primary ICH	2	Patient died 13 days after COVID-19 was diagnosed.
Haddadi et al. [46]	1 ICH	Female	54	1	0	0	Bilateral basal ganglia ICH	Primary ICH	5	–
Flores et al. [47]	1 ICH	Male	40	1	0	0	Midbrain and Pons with intraventricular extension	Primary ICH	NR	
Fraiman et al. [48]	1 ICH	Female	38	NR	0	NR	Frontal lobe	Primary ICH	0	Prior MRI showed microbleeds.
Rajdev et al. [49]	1 ICH	Male	62	1	1	1 - Heparin	NR	Possibly secondary due to HT of ischemic stroke.	12	Patient expired after 27 days of hospitalization
Hussain et al. [50]	1 ICH	Female	69	NR	1	1 - LMWH	NR	Primary ICH	24	Patient also had aortic vavle endocarditis Patient expired 18 days after admission
Krett et al.	1 ICH	Male	69	1	1	NR	Multifocal	Secondary to	17	Patient gradually recovered.

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Table 1 (*continued*)

Study	Number of intracranial hemorrhages/total number of cases with COVID-19 (n of ICH)	Sex (male) n	Age in years	History of HTN n	ICU admission prior to hemorrhage	Anticoagulation therapy at the time of ICH n	Hemorrhage location n	Etiology of hemorrhage	Days from COVID-19 to stroke diagnosis Median (range)	Other Findings
[51] Dixon et al. [52]	1 ICH	Female	59	NR	1	NR	Lobar (occipital lobe and later brain stem and amygdalae)	encephalopathy Secondary to acute necrotizing encephalopathy	10	History of transfusion dependent aplastic anemia

[a] n = number, ICH: Intracerebral Hemorrhage, SAH: Subarachnoid hemorrhage, SD: Standard Deviation, HTN: Hypertension, HT: Hemorrhagic Transformation, NR: Not Reported, IV: Intravenous, UFH: Unfractionated Heparin, LMWH: Low Molecular Weight Heparin, ECMO: Extracorporeal Membrane Oxygenation.

rhagic transformation of ischemic stroke, [18,39,42,49] 7 to cerebral vein thrombosis, [29,31] and 3 to encephalitis/encephalopathy [40,51,52].

Location of ICH was reported in 114 cases; 64 (56%) were located at lobar regions, 7 at deep/basal-ganglia, 13 supratentorial (not specified in detail), 13 infratentorial (1 midbrain & pons, 1 pons, 3 cerebellar, 8 not specified in detail), 7 non-lobar (not specified in detail) and 10 were reported as multifocal [2,19–23,26,27,29–48,51,52].

3.7. Mortality

Available data from 5 studies with known in-hospital mortality in patients with intracranial hemorrhage, showed that 49 (52.7%) out of 93 patients deceased [18,19,21–23].

4. Discussion

ICH is an infrequent but life-threatening complication of COVID-19. In our current literature review, incidence ranged from 0.14% to 0.86% in hospitalised patients with COVID-19. This rate is clearly higher than the worldwide incidence of ICH which is 24,6/100.000 person-years or 0,0246% per person-year [53] Even though COVID-19 equally affects both genders, European studies have shown a 3-fold to 4-fold higher incidence of ICU admission in male patients [54]. The fact that 61% of ICH cases were developed in ICU care, may explain the predominance of males.

4.1. Potential mechanisms of SARS-CoV-2 mediated cerebrovascular injury

A proposed mechanism of ICH is through a virus related direct and indirect endothelial injury. The virus can directly invade host's cells (in this case endothelial cells) via ACE2 receptor connection, causing cellular death. The indirect mechanism involves systemic factors such as inflammatory cytokine production, prothrombotic factors, activation of coagulation cascades, and complement-mediated microvascular thrombosis [2]. This thrombotic state has the potential of inducing ICH [55]. Finally, dysfunction of the blood–brain-barrier via tight junction complex disruption will occur leading to intracerebral hemorrhage [56].

4.2. Risk factors for intracerebral hemorrhage regardless of COVID-19 infection

The majority of patients with COVID-19 who developed ICH, had one or more risk factors such as arterial HTN, anticoagulation therapy or admission to the ICU due to severe disease. Acute spontaneous ICH is a common cause of critical illness and death among patients admitted to the ICU (regardless of COVID-19), making admission to the ICU a clearly important risk marker for the development of ICH [57]. Furthermore, SARS-CoV-2 can cause thrombotic events by both enhancing coagulation and weakening anticoagulation/fibrinolysis pathways [58]. Prothrombotic mechanisms have also been implied in the etiopathogenesis of ischemic strokes and are also observed in such patients; [58] with incidence ranging from 0,2% [59] to 1,4% [12]. Use of anticoagulants in acute ischemic stroke increases the risk of hemorrhagic transformation, which in our review was observed in 29 out of 188 ICHs.

The hypercoagulable state of SARS-CoV-2 combined with the high risk of thrombotic complications in critically ill patients admitted to ICU [60] makes pharmacological thromboprophylaxis or anticoagulation imperative in such cases; [61] mainly with the use of unfractionated heparin, LMWH, or fondaparinux; [62] furthermore, anticoagulation therapy appears to be independently

associated with ICH [63]. Lastly, ECMO, which can be applied in severe refractory COVID-19 pneumonia, may be a contributing factor to the development of ICH [63,64].

Arterial HTN can cause deep perforator arteriopathy/ hypertensive arteriolosclerosis, and is the most common cause of primary ICH located in deep brain structures [65,66]. In our review, arterial HTN does not appear to be the main cause of ICH as only 7 out of 114 hemorrhages were located in deep brain structures indicating etiopathogenetic mechanisms other than arterial HTN, at least for the majority of cases.

Other risk factors for ICH should be accounted for, but were not reported by the studies that we reviewed. For instance, brain hemorrhage in COVID-19 has been associated with an unusual pattern of cerebral microbleeds in critically ill patients [67–70]. Small vessel disease (most commonly cerebral amyloid angiopathy), aneurysms, arteriovenous malformations, brain tumors, alcohol abuse and genetic contribution could also be considered as contributing factors [71].

4.3. Clinical presentation of intracerebral hemorrhage

Time between onset of COVID-19 symptoms and development of ICH diagnosis varied; a median time of 1 or 1.5 days was observed in some studies [20,27] and up to 32 in other [2]. This variability could be partly explained by the deep sedation of patients admitted in ICU, which masks the typical symptoms of ICH. Physicians should strongly suspect the possibility of ICH in individuals with severe COVID-19 admitted to ICU and treated with anticoagulants.

4.4. Outcome

Typically, non-traumatic ICH is life-threatening emergency. Mortality reaches 40% at the first month and can rise up to 54% at 12 months [71,72]. Mortality in patients with ICH and COVID19 has not been reported in detail; data from our review show an in-hospital mortality of 52.7%; unfortunately no data are available for longer term follow–up. Of note, COVID-19 mortality in patients admitted in ICU is high (up to 49%) regardless of ICH development [73]. Finally, it is unclear whether ICH is related directly to COVID-19 or reflects expected comorbidity and/or complications observed in severely ill patients.

4.5. Limitations

Intracranial hemorrhage was used as a broader term in some reports and these patients could not be classified more specifically. Thus, SAH and other types of brain hemorrhage (i.e. primary intraventricular, subdural) are considered a confounding factor in our review. Publication bias was also an issue.

5. Conclusion

ICH is a rare clinical manifestation with high mortality rate in patients with COVID-19. Beyond typical risk factors for ICH, pathophysiologic involvement of SARS-CoV-2 can also be implicated. Although almost half of the reported cases had a history of arterial HTN, ICHs were mainly lobar, indicating other mechanism than hypertensive arteriolosclerosis. Admission to the ICU due to critical illness and the concomitant medical thromboprophylaxis or anticoagulation treatment seem clearly related with ICH. Still, it is unclear whether ICH is related directly to COVID-19 or reflects expected comorbidity and/or complications observed in severely ill patients. More original studies are needed in order to establish a clear relationship between ICH and COVID-19.

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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