Intracranial hemorrhage in coronavirus disease 2019 (COVID-19) patients

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Abstract

Background. Emerging evidence suggests that a subset of coronavirus disease 2019 (COVID-19) patients may present with or develop cerebrovascular disease during the course of hospitalization. Whereas ischemic stroke in COVID-19 patients has been well described, data on intracranial hemorrhage (ICH) in these patients is still limited. We, therefore, conducted a rapid systematic review of current scientific literature to identify and consolidate evidence of ICH in COVID-19 patients.

Methods. A systematic search of literature was conducted between November 1, 2019, and August 14, 2020, on PubMed and China National Knowledge Infrastructure (CNKI) to identify eligible studies.

Results. A total of 23 studies describing ICH in 148 COVID-19 patients were included. The pooled incidence of ICH in COVID-19 patients was 0.7% (95% CI 0.5–0.9), with low levels of inter-study heterogeneity observed (I² = 33.6%, Cochran’s Q = 12.05, p = 0.149). Most of the patients were elderly male patients (65.8%) with comorbidities, the most common being systemic hypertension (54%). Hemorrhage involving multiple cranial compartments was reported in 9.5% of cases. Single compartments were involved in the rest, with intraparenchymal hemorrhage (IPH) being the most common variety (62.6%) and intraventricular hemorrhage (IVH) the least common (1.4%). Half of these patients were on some form of anticoagulation. Overall, the mortality rate in the COVID-19 patients with ICH was about 48.6%.

Conclusion. Although relatively uncommon among COVID-19 patients, ICH is associated with a high mortality rate. Early identification of patients at risk of developing ICH, particularly with comorbid conditions and on anticoagulant therapy, may be important to improve outcomes.

Keywords. COVID-19 · Intracranial hemorrhage · Hemorrhagic stroke

Introduction

Recent reports have highlighted the relationship between coronavirus disease 2019 (COVID-19) and cerebrovascular disease (CVD). Past history of CVD has been associated with poor outcomes among COVID-19 patients [1–3]. On the other hand, a subset of these patients develops CVD during the course of hospitalization [4, 5]. Whereas ischemic CVD, which has been attributed to a hypercoagulable state characterized by micro- and macrovascular thrombotic angiopathy [6, 7], is more common and is described in literature [4, 5, 8, 9], reports on hemorrhagic CVD in these patients are few and scattered [10–13]. We, therefore, conducted a rapid systematic review of current scientific literature to identify and consolidate data on the incidence, age and sex distribution, clinical presentation, types, and clinical outcomes of intracranial hemorrhage (ICH) in COVID-19 patients.

Methods

A rapid systematic review of scientific literature was conducted to consolidate currently available data on intracranial
hemorrhage (ICH) in COVID-19 patients. Rapid reviews accelerate the process of evidence synthesis while maintaining a systematic approach.

**Literature search strategy**

A comprehensive and systematic search of literature from November 1, 2019, to August 14, 2020, was conducted on the Medline (PubMed interface) and China National Knowledge Infrastructure (CNKI) to identify studies eligible for inclusion. The electronic search was carried out Boolean operators and using the strategy as follows: (COVID-19) AND (((((((stroke) OR (hemorrhagic stroke)) OR (intracerebral hemorrhage)) OR (subarachnoid hemorrhage)) OR (cerebrovascular disease)) OR (neurological manifestation))). No language restriction was applied. When the articles were published by the same study group and there was an overlap of the search period, only the most recent article was included to avoid duplication of data. The PubMed function “related articles” was used to extend the search. Also, we searched major infectious disease, neurology, and general medicine journals reporting articles about COVID-19 infection to identify additional studies. We then performed hand-search of the bibliography of included studies, to detect other potentially eligible investigations.

**Eligibility criteria**

The search results were screened by title and abstract, with those of potential relevance evaluated by full text. Studies were deemed eligible for inclusion if they fulfilled the following criteria: (1) were case reports/case series/cohort studies, (2) included patients with a reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed COVID-19 diagnosis, (3) monitored the patients for development of complications during the course of admission, and (4) reported clear extractable data on hemorrhagic stroke.

**Data extraction**

Data extraction was conducted by two independent reviewers (I.C and B.N). For each study, the following information was extracted: the surname of the first author and the year of publication, country where the study was performed, the type of study (case report/case series/cohort), sample size, demographic characteristics, number of patients with intracranial hemorrhage, type of intracranial hemorrhage, anticoagulation prior to onset of hemorrhagic event, comorbidities, and mortality rate. Any variances arising during this were resolved by a consensus.

**Synthesis of findings**

Synthesis of results was carried out in two steps. First, findings on all eligible studies reporting intracranial hemorrhage in COVID-19 patients were presented in the form of a summary of findings table (Table 1) accompanied by a narrative description. Thereafter, a pooled analysis incorporating only cohort studies in which all hospitalized patients were studied within a specified period of time was conducted to estimate pooled incidence of intracranial hemorrhage in COVID-19 patients using the Meta-Analyst (software version 5.26.14, Center for Evidence-Based Medicine, Brown University, Providence, USA). A random effects model was applied. The magnitude of heterogeneity among the included studies was assessed using the chi-square test (Chi2) and I-squared statistic ($I^2$). For the Chi2 test, a Cochrane’s $Q$ p value of < 0.10 was considered significant. An $I^2$ of < 40% was considered not significant. Additionally, a leave-one-out sensitivity analysis was performed to assess the robustness of the results and to further probe the sources of inter-study heterogeneity.

**Results**

**Study identification**

The initial search produced 999 potentially relevant articles. Following the removal of duplicates and primary screening, 54 articles were assessed by full text for eligibility in the meta-analysis. Of these, 31 were excluded because the primary and secondary outcome of the study did not match that of this review. Thus, a total of 23 articles were included in this systematic review and meta-analysis (Fig. 1 and Table 1).

**Characteristics of the included studies**

A total of 23 studies describing intracranial hemorrhage (ICH) in 148 COVID-19 patients were included [10–32]. Majority of the studies were from North America (USA, 9 studies) and Europe (8 studies). The rest were from the Middle East (4 studies) and Asia (2 studies). Of the included studies, twelve were cohort, six were case series, while the rest were case reports. Essential characteristics of the included are outlined in Table 1.

**Data synthesis**

**Incidence of intracranial hemorrhage in COVID-19 patients**

Nine cohort studies ($n = 13,741$ patients) reported data on the incidence of intracranial hemorrhage (ICH) in COVID-19 patients, with the incidence ranging from 0.3 to 1.2% [10, 13, 16, 19–22, 26, 28]. The pooled incidence of ICH across these nine
| Author               | Setting | Type of study | Sample size | No. with hemorrhagic cerebrovascular disease | Type of hemorrhagic event | Age and sex composition of the patient(s) | Initial symptoms (neurologic vs respiratory) | Time interval between COVID-19 and stroke | Comorbid conditions | Anticoagulation prior to stroke? | Outcome |
|---------------------|---------|---------------|-------------|---------------------------------------------|---------------------------|------------------------------------------|---------------------------------------------|-------------------------------------------|------------------------------------------|------------------------------------------|---------|
| Al-olama 2020       | UAE     | Case report   | 1           | 1                                           | IPH (lobar) and SDH SAH   | M, 36 years M, 31 years                  | Respiratory Respiratory                     | 5 days 1 week                             | None None None None                    | Survival                             |
| Al-Saiegh 2020      | USA     | Case series   | 2           | 1                                           | IPH (bilateral basal ganglia) IPH (lobar) | F, 54 years F, 58 years                  | Respiratory                                | 5 days 19 and 13 days, respectively     | DM, HTN DM, SLE HTN, OSA Heparin for VV-ECMO (within therapeutic range) | Survival |
| Haddadi 2020        | Iran    | Case report   | 1           | 1                                           | IPH (lobar) IPH (cerebellar and cerebral lobar) | M, 60 years M, 57 years M, 57 years | Respiratory                                | 10 days 7 days and 22 days, respectively | HTN HTN None in the 2nd patient None in the 2nd patient | Death in both patients |
| Herman-Acka 2020    | USA     | Case series   | 2           | 2                                           | IPH (lobar) with ventricular extension (pericallosal aneurysm) | F, 60 years | Neurologic Not reported | Not reported Not reported None | None None None None | Death in both patients |
| Mao 2020            | China   | Cohort        | 214*        | 1                                           | IPH (lobar) | M, 60 years M, 57 years M, 57 years | Respiratory                                | 10 days 19 and 13 days, respectively     | HTN HTN None in the 2nd patient None in the 2nd patient | Death in both patients |
| Morassi 2020        | Italy   | Case series   | 6           | 2                                           | IPH (lobar) | IPH (cerebellar and cerebral lobar) | Respiratory                                | 10 days 7 days and 22 days, respectively | HTN HTN None in the 2nd patient None in the 2nd patient | Death in both patients |
| Muhammad 2020       | Germany | Case report   | 1           | 1                                           | IPH (lobar) with ventricular extension (pericallosal aneurysm) | F, 60 years | Neurologic Not reported | Not reported Not reported None | None None None None | Survival |
| Romero-Sánchez 2020 | Spain   | Cohort        | 841*        | 3                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Therapeutic heparin (for elevated D-dimers) Not reported | Death in both patients |
| Scullen 2020        | USA     | Cohort        | 27**        | 3                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported | Not reported |
| Sharif-Razavi 2020  | Iran    | Case report   | 1           | 1                                           | MCH (IPH [lobar], IVH & SAH IPH (lobar, 4 patients; basal ganglia bleed; 1 patient); SAH (2 patients)) | M, 79 years | Respiratory | 3 days None | None None | Not reported |
| Hernández-Fernández 2020 | Spain | Cohort        | 1683*       | 5                                           | MCH (IPH [lobar], IVH & SAH IPH (lobar, 4 patients; basal ganglia bleed; 1 patient); SAH (2 patients)) | 51, 61, 64, 68 and 69 years; 1 female and 4 males | Respiratory in 4 patients; neurologic in 1 patient | 12 days (median) HTN (4 patients); DM and dyslipidemia (2 patient) | 3 on enoxaparin 1 mg/kg/twice a day | Death in 2 patients (40%) |
| Karadas 2020        | Turkey  | Cohort        | 239*        | 2                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Not reported | Death |
| Li 2020             | China   | Cohort        | 219*        | 1                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Not reported | Not reported |
| Pinna 2020          | USA     | Case series   | 650*        | 8                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Not reported | Not reported |
| Pons-Escoda 2020    | Spain   | Cohort        | 112**       | 7                                           | IPH (lobar, 4 patients; basal ganglia hemorrhage, 3 patients) | 6 males; 1 female Age: 49–78 years | Respiratory | 3 days None | None None | Not reported |
| Reddy 2020          | USA     | Case series   | 12           | 2                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Not reported | Death |
| Sweid 2020          | USA     | Case series   | 22           | 3                                           | SAH (PIVM, PComm, and ACA aneurysms) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Not reported | Not reported |
| UK                  | Cohort  |          | 153**       | 9                                           | IPH (lobar) | IPH (lobar) | Respiratory | Not reported Not reported Not reported Not reported | Not reported Not reported | Not reported |
Table 1 (continued)

| Author          | Setting                  | Type of study | Sample size | No. with hemorrhagic cerebrovascular disease | Type of hemorrhagic event | Age and sex composition of the patient(s) | Initial symptoms (neurologic vs respiratory) | Time interval between COVID-19 and stroke | Comorbid conditions | Anticoagulation prior to stroke? | Outcome |
|-----------------|--------------------------|---------------|-------------|---------------------------------------------|---------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------|--------------------------------------|----------|
| Varatharaj 2020 | USA Cohort*              | 5227          | 35          | SDH (17 patients); SAH (2 patients); MCH (7 patients); IPH (lobar) (9 patients) | 21 males, 14 females Median age: 67 years | Not reported | Not reported | HTN (25 patients); DM (10 patients); CHF (6 patients); CAD (2 patients) | Anticoagulation in 7 patients | Death in 16 patients (45.7%) |
| Altschul 2020   | USA Cohort*              | 3824          | 33          | IPH (lobar)                                  | 26 males, 7 females Mean age: 61.6 years | Respiratory, 29 patients; neurologic, 4 patients | 17 days (median) | HTN (12 patients); DM (10 patients); CAD (4 patients); dyslipidemia (12 patients) | Anticoagulation in 22 patients | Death in 14 patients (42.4%) |
| Dogra 2020      | USA Cohort*              | 10            | 1           | IPH (lobar)                                  | 75 years                   | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | HTN (6 patients); DM (3 patients); dyslipidemia (5 patients); CAD (3 patients); obesity (3 patients) | Anticoagulation for VV-ECMO in 4 patients | Death in 6 patients (76%) |
| Mehpour 2020    | Iran Case series         | 844           | 8           | IPH (lobar) (5 patients); SAH (3 patients) | 4 males, 4 females Mean age 57 ± 7 | Respiratory symptoms in all | 25 days | HTN (6 patients); DM (3 patients); dyslipidemia (5 patients); CAD (3 patients); obesity (3 patients) | Anticoagulation for VV-ECMO in 4 patients | Death in 6 patients (76%) |
| Nawabi 2020     | Germany, France, and Switzerland Cohort** | 18            | 18          | SDH (1 patient); IVH (3 patients); SAH (13 patients); IPH (lobar) (6 patients) | 9 males, 9 females Median age: 49.50 years | Not reported | Not reported | Not reported | HTN (10 patients); DM (4 patients) | Anticoagulation in 8 patients | Death in 8 patients (44.4%) |
| Rothstein 2020  | USA Cohort*              | 5227          | 35          | SDH (17 patients); SAH (2 patients); MCH (7 patients); IPH (lobar) (9 patients) | 21 males, 14 females Median age: 67 years | Not reported | Not reported | HTN (25 patients); DM (10 patients); CHF (6 patients); CAD (2 patients) | Anticoagulation in 7 patients | Death in 16 patients (45.7%) |

MCH multicompartamental hemorrhage, IPH intraparenchymal hemorrhage, IVH intraventricular hemorrhage, SAH subarachnoid hemorrhage, PICA posterior inferior cerebellar artery, PComm posterior communicating artery, SDH subdural hemorrhage, M male, HTN hypertension, DM diabetes mellitus, SLE systemic lupus erythematosus, OSA obstructive sleep apnea

*All hospitalized COVID-19 patients were included in the study

**Only COVID-19 patients with neurologic complications were included
studies was 0.7% (95% CI 0.5–0.9), with low levels of inter-study heterogeneity observed ($I^2 = 33.6\%$, Cochran’s Q = 12.05, $p = 0.149$) (Fig. 2). No significant changes in the pooled incidence were observed in the leave-one-out sensitivity analysis.

Age and sex distribution of COVID-19 patients with intracranial hemorrhage

Majority of the COVID-19 patients with intracranial hemorrhage were male (65.8%). The reported age of these patients ranged from 31 to 78 years. Across all case reports and case series, only 16% of patients were < 50 years old. The mean or median age of the patients was > 50 years in all but one cohort study.

Types of intracranial hemorrhage among COVID-19 patients

Hemorrhage involving multiple cranial compartments (MCH) was reported in 14 cases (9.5%). Single compartments were involved in the rest, with intraparenchymal hemorrhage (IPH) being the most common variety (62.6%), followed by subarachnoid hemorrhage (SAH) (15.0%), subdural hemorrhage (SDH) (11.6%), and intraventricular hemorrhage (IVH)
(1.4%). In patients with IPH, the most location of the bleed was the cerebral lobes (93.5%). Other sites included basal ganglia (5.4%) and cerebellum (1.1%).

Initial symptom (respiratory vs neurologic)

Majority (71%) of the patients were admitted due to respiratory symptoms of COVID-19 and developed the intracranial hemorrhage (ICH) in their course of admission. The interval between the onset of respiratory symptoms and diagnosis of ICH ranged from 2 to 25 days. The rest (21%) were admitted due to neurological symptoms, such as acute loss of consciousness and sudden onset severe headache, and were later confirmed to have COVID-19 through RT-PCR tests.

Comorbid conditions in the COVID-19 patients with intracranial hemorrhage

Majority of the patients had pre-existing illnesses such as hypertension [10–12, 16–19, 21, 22, 25, 27, 28], diabetes mellitus (DM) [10, 16–19, 25, 27, 28], hyperlipidemia [16, 19, 27, 28], coronary artery disease (CAD) [10, 16, 28], obesity [28], congestive heart failure (CHF) [10], obstructive sleep apnea (OSA) [18], and systemic lupus erythematosus (SLE) [18].

Anticoagulation prior to onset of intracranial hemorrhage

Data on anticoagulation in COVID-19 patients prior to onset of ICH was reported in 8 (n = 114 patients) [10, 11, 16, 18, 19, 25, 28, 29]. Overall, 58 patients (50.9%) were on some form of anticoagulation. The indication for anticoagulation was part of in-hospital treatment for COVID-19 (standard prophylaxis [11, 16, 18, 19], elevated D-dimers [16, 29], and extracorporeal membrane oxygenation (ECMO) [25, 28]) in majority of these patients (84%). The rest were on therapeutic anticoagulation for non-COVID-19 indications [10, 16].

Mortality in COVID-19 patients with intracranial hemorrhage

Across the 14 studies (n = 111 patients) (Table 1) that reported data on mortality in COVID-19 patients with ICH, the mortality rate was 48.6%.

Discussion

This review of the literature provides a comprehensive and systematic analysis of intracranial hemorrhage (ICH) in COVID-19 patients. The incidence of ICH was found to be 0.7% (95% CI 0.5–0.9), which is lower than the incidence of ischemic stroke which has been reported to develop in about 1.2% of these patients [33].

The role of the severe acute respiratory syndrome 2 (SARS-CoV-2) virus in the development of ICH in COVID-19 patients is still unclear. Majority of these patients had classic Framingham risk factors such as advanced age, being male, and pre-existing illnesses such as hypertension and diabetes mellitus, which are well-established risk factors for vascular degenerative changes, that could have predisposed them to the development of ICH [34, 35]. Further, a significant proportion of patients were on some form of anticoagulation therapy, which could have predisposed them to the development of ICH. This is consistent with a recent retrospective study of 3824 COVID-19 patients by Melmed and colleagues [36] in which anticoagulation was associated with a 5-fold increase (OR = 5.26, 95% CI 2.22–12.24) in the risk of ICH. The association between anticoagulation and risk of ICH in COVID-19 patients was confirmed. Some of the patients however had no prior illnesses or risk factors that could explain the ICH [14, 15], leading to speculations about possible causal role of the SARS-CoV-2 virus.

Several hypotheses have subsequently been put forward. First, it has been postulated that SARS-CoV-2 is neutropic [37, 38] and can invade and directly damage cerebral blood vessels, facilitated by the overexpression of angiotensin converting enzyme 2 (ACE2) [39, 40], the viral entry protein for SARS-CoV-2, within vascular endothelium. This may result in endothelialitis, characterized histologically by diffuse endothelial damage and mononuclear infiltration [40]. This hypothesis is further supported by recent electron microscopic studies that have demonstrated the presence of viral inclusion particles within the endothelium, and viral RNA detection in cerebrospinal fluid [41, 42]. Second, entry of the SARS-CoV-2 virus into cells results in marked reduction in ACE-2 levels [43]. Since this protein usually catalyzes conversion of angiotensin II to counter-regulatory angiotensin 1-7 [44, 45], reduction in its levels results in enhanced and unopposed effects of angiotensin II via the ACE-angiotensin II-AT1 receptor axis [43–45]. These effects, mediated by angiotensin II, vasopressin, and aldosterone, include vasoconstriction, water and sodium reabsorption, as well as vascular wall inflammation [45], all of which could contribute to development of ICH. This is supported by pre-clinical studies in which an inverse relationship between ACE2 levels and the occurrence of hypertension has been observed [46]. Clinical studies have also highlighted on adverse blood pressure changes in COVID-19 patients. For instance, Vicenzi et al. [47] in their study of 40 COVID-19 patients demonstrated significant rise in the systemic blood pressure with deterioration in the pulmonary function, even in patients without prior history of hypertension. Third, a subset of COVID-19 patients usually develops a systemic hyperinflammatory syndrome characterized by fulminant hypercytokinemia [48, 49], which may mediate vascular
remodeling and predispose to ICH. The pro-inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) are potent activators of matrix metalloproteinases (MMPs), a group of proteolytic enzymes that degrade elastin, collagen, and other components of the extracellular matrix (ECM) [50]. Such alterations result in loss of vascular wall integrity, increasing risk of rupture and hemorrhage, as has been well documented in other vascular degenerative diseases such as aortic aneurysms [51]. The cytokines may also activate the coagulation cascade, resulting in thrombotic microangiopathy (TMA) of the vasa-vasora which may result in arterial wall hypoxia, undermining vascular integrity and leading to rupture [52].

Our findings suggest that COVID-19 patients who develop ICH experience poor outcomes, with mortality rates of approximately 49%. This is largely reflective of the distribution of patients at risk of developing ICH, particularly with comorbid conditions and on anticoagulant therapy, may be important to improve outcomes.

Our study was limited by the small number of included studies, some of which mainly case reports and case series. There was insufficient data to perform meta-regression on incidence of ICH. Larger studies are needed to corroborate these findings.

**Conclusion**

Although relatively uncommon among COVID-19 patients, ICH is associated with a high mortality rate. Early identification of patients at risk of developing ICH, particularly with comorbid conditions and on anticoagulant therapy, may be important to improve outcomes.

**Data availability** Data is available at reader’s request.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**References**

1. Aggarwal G, Lippi G, Michael Henry B (2020) Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature. Int J Stroke 15(4):385–389
2. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M et al (2020) Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 55(5):2000524
3. Pranata R, Huang I, Lim MA, Wahjoipramono EJ, July J (2020) Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19-systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 29(8):104949
4. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM et al (2020) Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 191:148–150
5. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Alexia B, Sandri MT, Barco S, Humanitas COVID-19 Task Force (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 191:9–14
6. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stolzrus A, Laurence J (2020) Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Trans Res 220:1–13
7. Panigada M, Bottino N, Tagliaube P, Grasselli G, Novembrino C, Chantarangkul V, Pesenti A, Peyvandi F, Tripodi A (2020) Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 18:1738–1742
8. Thomas W, Varley J, Johnston A, Symington E, Robinson M, Sheares K, Lavinio A, Besser M (2020) Thrombotic complications of patients admitted to intensive care with COVID-19 at a teaching hospital in the United Kingdom. Thromb Res 191:76–77
9. Viguier A, Delamarre L, Duplantier J, Olivot J-M, Bonneville F (2020) Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. J Neurol 267(5):393–394
10. Altschul DJ, Unda SR, de La Garza RR, Zampolin R, Benton J, Holland R et al (2020) Hemorrhagic presentations of COVID-19: risk factors for mortality. Clin Neurol Neurosurg 198:106112
11. Morassi M, Bagatto D, Cobelli M, D’Agostini S, Gigli GL, Bná C, Vogrig A (2020) Stroke in patients with SARS-CoV-2 infection: case series. J Neurol 267(8):2185–2192
12. Reddy ST, Reddy ST, Targ T, Shah C, Nascimento FA, Imran R et al (2020) Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. Case Rep Neurol 7:10.1212/WNL.0000000000009937
15. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen A, Layos-Romero A, García-García J, González E, Redondo-Peñas I, Perona-Moratalla AB, del Valle-Pérez JA, Gracia-Gil J, Rojas-Bartolomé L, Ferrà-Vilar I, Montagudo M, Palao M, Palazón-García E, Alcañiz-Rodríguez C, Sopelana-Garay D, Moreno Y, Ahmad J, Segura T (2020) Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology 95:e1060–e1070. https://doi.org/10.1212/WNL.0000000000009937
14. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T et al (2020) Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J Neurol Neurosurg Psychiatry 91(8):1–3
15. Al-olama M, Rashid A, Garozzo D (2020) COVID-19-associated meningoencephalitis complicated with intracranial hemorrhage: a case report. Acta Neurochir 162(7):1495–1499

16. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, Lewis A, Melmed K, Hochman K, Horwitz L, Galeta S, Berger J (2020) Hemorrhagic stroke and anticoagulation in COVID-19. J Stroke Cerebrovasc Dis 29(8):104948

17. Haddadi K, Ghashemian R, Shafizad M (2020) Basal ganglia involvement and altered mental status: a unique neurological manifestation of coronavirus disease 2019. Cureus 12(4):e7869

18. Heman-Ackah SM, Su YRS, Spadola M, Petrov D, Chen HI, Su YRS, Spadola M, Petrov D, Chen HI, Haddadi K, Ghasemian R, Shafizad M (2020) Basal ganglia involvement and altered mental status: a unique neurological manifestation of coronavirus disease 2019. Cureus 12(4):e7869

19. Hall E, Oldridge O, Schwennesen H, Do D, Cucchiara BL (2020) Coronavirus disease 2019: a neurovascular complication. J Neurol Sci 421(May):116969

20. Karadas Ö, Öztürk B, Sonkaya AR (2020) A prospective clinical study of detailed neurological manifestations in patients with COVID-19. Neurol Sci 41(8):1991–1995

21. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y et al (2020) Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 5(3):1–6

22. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhu, China. JAMA Neurol 77(6):683–690

23. Mehrpour M, Shuaib A, Farahani M, Hatamabadi H, Fatehi Z, Ghaffari M et al (2020) Coronavirus disease 2019 and stroke in Iran: a case series and effects on stroke admissions. Int J Stroke (online). https://doi.org/10.1177/1747493020937397

24. Muhammad S, Petridis A, Cornelius JF, Hanggi D (2020) Letter to editor: severe brain haemorrhage and concomitant COVID-19 infection: a neurovascular complication of COVID-19. Brain Behav ImmuN 87:150–151

25. Navabi J, Morotti A, Wildgruber M, Boulouis G, Kraehling H, Al-olama M, Rashid A, Garozzo D (2020) COVID-19: understanding the neurological manifestations in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 7:875–882

26. Tan Y-K, Goh C, Leow AST, Tambyah PA, Ang A, Yap E-S et al (2020) COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. J Thromb Thrombolysis 50(3):587–595

27. Yachou Y, El Idrissi A, Belapasov V, Ait BS (2020) Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients. Neurol Sci 41:2657–2669

28. Zhou Z, Kang H, Li S, Zhao X (2020) Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol 267(8):2179–2184

29. Bermejo-Martin J, Almansa R, Torres A, Gonzalez-Revera M, Kelvin DJ (2020) Available from: COVID-19 as cardiovascular disease: the potential role of chronic endothelial dysfunction [Internet]. Cardiovasc Res 116:e132–e133. https://doi.org/10.1093/cvr/evy147

30. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G (2020) Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. J Clin Med 9(5):1417

31. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myone N, Nakao A, Takeda M, Haro H, Inoue O, Suzuki-Inoue K, Kubokawa K, Ogihara S, Sasaki T, Kinouchi H, Kojin H, Ito M, Onishi H, Shimizu T, Sasaki Y, Enomoto N, Ishihara H, Furuya S, Yamamoto T, Shimada S (2020) A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis 94:55–58

32. Zhou L, Zhang M, Wang J, Gao J (2020) Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7269702/ Sars-Cov-2: underestimated damage to nervous system. Travel Med Infect Dis 36:101642

33. Silhol F, Sarlon G, Deharo J-C, Vaïsse B (2020) Downregulation of ACE2 induces overstimulation of the renin–angiotensin system in...
COVID-19: should we block the renin–angiotensin system? Hypertens Res 43(8):854–856

44. Ciulla MM (2020) SARS-CoV-2 downregulation of ACE2 and pleiotropic effects of ACEIs/ARBs. Hypertens Res 43(9):985–986

45. Verdecchia P, Cavallini C, Spanevello A, Angeli F (2020) The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 76:14–20

46. Alenina N, Bader M (2019) ACE2 in brain physiology and pathophysiology: evidence from transgenic animal models. Neurochem Res 44(6):1323–1329

47. Vicenzi M, Cosola RD, Ruscica M, Ratti A, Rota F et al (2020) The liaison between respiratory failure and high blood pressure: evidence from COVID-19 patients. Eur Respir J 56:2001157 [Internet]. [cited 2020 Sep 21]; Available from: https://erj.ersjournals.com/content/early/2020/05/13/13993003.01157-2020

48. Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A et al (2020) COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. Neuroscientist 26(5-6):402–414

49. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 395(10229):1033–1034

50. Sprague AH, Khalil RA (2009) Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem Pharmacol 78(6):539–552

51. Thompson RW, Parks WC (1996) Role of matrix metalloproteinases in abdominal aortic aneurysms. Ann N Y Acad Sci 800:157–174

52. Martin JF, Booth RFG, Moncada S (1991) Arterial wall hypoxia following thrombosis of the vasa vasorum is an initial lesion in atherosclerosis. Eur J Clin Invest 21(3):355–359

53. Al-Mufti F, Thabet AM, Singh T, El-Ghanem M, Amuluru K, Gandhi CD (2018) Clinical and radiographic predictors of intracerebral hemorrhage outcome. Interv Neurol 7(1–2):118–136

54. Katz JM, Libman RB, Wang JJ, Sanelli P, Filippi CG, Gribko M et al (2020) Cerebrovascular complications of COVID-19. Stroke 51(9):e227–e231

55. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J et al (2020) Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the global COVID-19 stroke registry. Stroke 51:e254–e258

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