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COVID-19

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 (I^2 = 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

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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

Table 1 Characteristics of the included studies

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	M, 36 years	Respiratory	5 days	None	None	Survival
Al-Saiegh 2020	USA	Case series	2	1	SAH (PICA aneurysm rupture)	M, 31 years	Respiratory	1 week	None	None	Survival
Haddadi 2020	Iran	Case report	1	1	IPH (bilateral basal ganglia)	F, 54 years	Respiratory	5 days	DM, HTN	None	Survival
Heman-Acka 2020	USA	Case series	2	2	IPH (lobar)	F, 58 years M, 46 years	Respiratory	19 and 13 days, respectively	DM, SLE HTN, OSA	Heparin for VV-ECMO (within therapeutic range)	Death in both patients
Mao 2020	China	Cohort	214*	1	IPH (lobar)	M, 60 years	Respiratory	10 days	HTN	None	Death
Morassi 2020	Italy	Case series	6	2	IPH (cerebellar and cerebral lobar)	M, 57 years M, 57 years	Respiratory	7 days and 22 days, respectively	HTN None in the 2nd patient	Prophylactic 4000 IU enoxaparin daily subcutaneous-ly	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	None	Survival
Romero-Sánchez 2020	Spain	Cohort	841*	3	Not reported	Not reported	Respiratory	Not reported	Not reported	Not reported	Not reported
Scullen 2020	USA	Cohort	27**	3	IPH (lobar)	Not reported	Respiratory	Not reported	Not reported	Therapeutic heparin (for elevated D-dimers)	Not reported
Sharif-Razavi 2020	Iran	Case report	1	1	MCH (IPH [lobar], IVH & SAH	M, 79 years	Respiratory	3 days	None	None	Not reported
Hernández-Fer-nández 2020	Spain	Cohort	1683*	5	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)	Not reported	Respiratory	Not reported	Not reported	Not reported	Not reported
Li 2020	China	Cohort	219*	1	IPH (lobar)	M, 60 years	Respiratory	10 days	HTN	Not reported	Death
Pinna 2020	USA	Case series	650*	8	IPH (lobar) (4 patients); SAH (non-aneurysmal) (4 patients)	Not reported	Respiratory (6 patients); neurologic (2 patients)	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	Not reported	HTN (4 patients); DM (2 patients); hypercholester-olemia (1 patient)	Not reported	Not reported
Reddy 2020	USA	Case series	12	2	IPH (lobar)	F, 60 years M, 48 years	Not reported	2 and 20 days, respectively	HTN and DM	Not reported	Death
Sweid 2020	USA	Case series	22	3	SAH (PICA, PComm, and ACA aneurysms)	Not reported	Respiratory	3 days, 9 days and 9 days, respectively	Not reported	None	Not reported
	UK	Cohort	153**	9	IPH (lobar)	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											
Altschul 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%)
Dogra 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%)
Mehpour 2020	Iran	Case series	10	1	IPH (lobar)	75 years	Not reported	Not reported	Not reported	Not reported	Not reported
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	Respiratory, 16 patients; neurologic, 2 patients	Not reported	HTN (10 patients); DM (4 patients)	Anticoagulation in 8 patients	Death in 8 patients (44.4%)
Rothstein 2020	USA	Cohort*	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%)

MCH multicompartmental 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

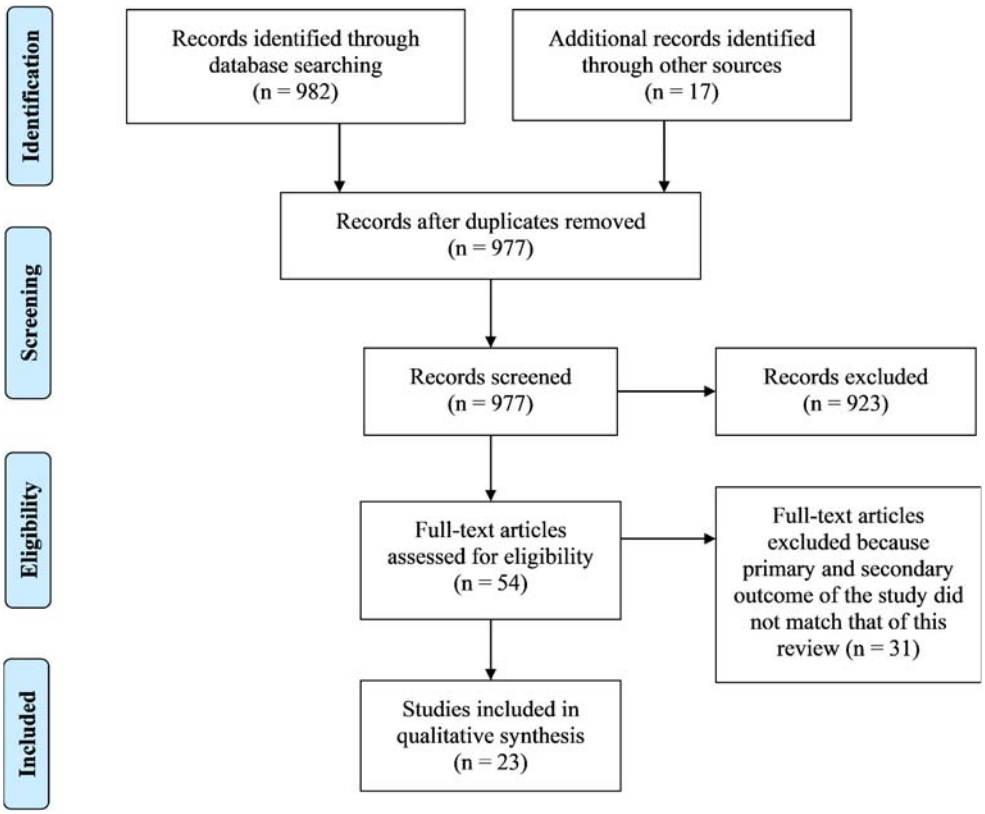

Fig. 1 PRISMA flow diagram indicating flow of studies through the review

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)

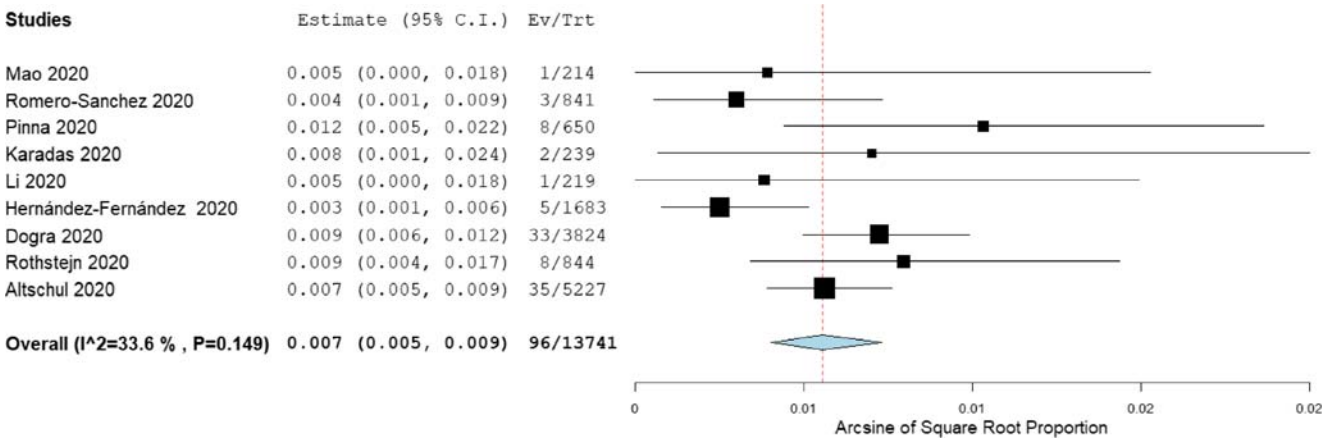

Fig. 2 Forest plot for the pooled incidence of intracranial hemorrhage in COVID-19 patients

(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 endotheliitis, 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 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 the various types of ICH observed in these patients, where intraparenchymal hemorrhage which are known to have less favorable outcomes [53] were the most common. Our findings are consistent with a recent retrospective cohort of 3824 COVID-19 patients in which ICH was associated with increased mortality (OR = 2.6, 95% CI 1.2–5.9) [36]. The mortality rate observed in this study is also consistent with recent studies in which COVID-19 patients with stroke were shown to have worse functional outcome and higher mortality rates than non-COVID-19 stroke patients [54, 55].

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.

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