COVID-19 and intracranial hemorrhage: a multicenter case series, systematic review and pooled analysis

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) profoundly impacts on hemostasis and microvasculature. Correspondingly, antithrombotic therapy is frequently used for prophylaxis or treatment of thromboembolic complications as well as in the context of extracorporeal membrane oxygenation (ECMO). However, reports of intracranial hemorrhage (ICH) associated with Coronavirus disease 2019 (COVID-19) have also emerged. In the light of the dilemma between thromboembolic and hemorrhagic complications, we sought to systematically investigate incidence, mortality, radiological subtypes and clinical characteristics of ICH in COVID-19 patients.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we performed a systematic review of literature by screening the PubMed database and included patients diagnosed with COVID-19 and concomitant ICH. Furthermore, we performed a pooled analysis including a prospectively collected cohort of critically ill COVID-19 patients with ICH as part of the PANDEMIC registry (Pooled Analysis of Neurologic Disorders Manifesting in Intensive care of COVID-19).

Results: Our literature review revealed a total of 217 citations. After selection process, 79 studies and a total of 477 patients were included. Median age was 58.8 years (95% CI 54.8 years-62.9 years; \(I^2 = 85.6\%\)). 23.3% patients experienced critical stage of COVID-19 (95% CI 8.9% − 61.2%, \(I^2 = 53.8\%\)). 62.7% patients were on anticoagulation (95% CI 38.2% − 103.0%, \(I^2 = 82.6\%\)), and 27.5% patients received ECMO (95% CI 5.8% − 130.2%, \(I^2 = 92.7\%\)). Microbleeds (51.1%, 95% CI 31.1% − 84.2%, \(I^2 = 85.1\%\)), subarachnoid hemorrhage (SAH) (26.6%, 95% CI 16.8% − 42.0%, \(I^2 = 61.2\%\)) and intraparenchymal hemorrhage (IPH) (33.7%, 95% CI 23.3% − 48.8%, \(I^2 = 63.7\%\)) were most frequently documented as ICH subtypes. Incidence was at 0.85% (95% CI 0.36%-1.99%; \(I^2 = 97.5\%\)) and mortality at 52.18% (95% CI 40.40%-67.39%; \(I^2 = 51.7\%\)), respectively.

Conclusion: ICH in COVID-19 patients is rare, but has a very poor prognosis. Different subtypes of ICH seen in COVID-19 support the assumption of heterogenous and multifactorial pathomechanisms contributing to ICH in COVID-19. Further data and pathophysiological insights are warranted to resolve the conflict between thromboembolic and hemorrhagic complications in the future.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), manifests most commonly as a respiratory disease. However, a growing body of clinical data show that neurological manifestations significantly contribute to the clinical spectrum of the disease and are especially relevant in critically ill patients.(1–3)

Besides other neurological manifestations, cerebrovascular disease has frequently been linked to acute SARS-CoV2 infection.(4–6) To account for the SARS-CoV2-associated hypercoagulable state, several
pathophysiological mechanisms have been proposed, including both direct and indirect effects of the viral infection. Apart from hypercoagulable features, SARS-CoV2-associated endothelitis and microangiopathy are also postulated to contribute to hemorrhagic stroke. Intracranial hemorrhage (ICH) in COVID-19 patients therefore might either be due to hemorrhagic transformation of ischemic stroke, primary hemorrhagic stroke or traumatic ICH. Accordingly, the relevance of SARS-CoV2 related effects for the pathogenesis of these ICH subtypes might be as heterogeneous.

As critically ill COVID-19 patients receive antithrombotic therapy in the majority of cases, including therapeutic range anticoagulation due to venous thromboembolism or extracorporeal membrane oxygenation (ECMO), the risk for ICH might be elevated. Also, the incidence of ICH in these patients might be underestimated since prolonged sedation in COVID-19 patients challenges valid neurological assessment to allow timely detection of potential focal-neurological deficits.

So far, only scarce data are available on ICH in COVID-19 patients. The existing literature mainly consists of case reports and case series and thus does not allow further conclusions. Previous reviews in COVID-19 cohorts only covered intraparenchymal hemorrhages (IPH), cerebrovascular disease in general or reported quite low numbers of patients, leaving a significant gap in understanding the relevance of ICH in COVID-19.

To examine the incidence, mortality, radiological subtypes and clinical characteristics associated with ICH in COVID-19 patients, we performed a systematic review of the relevant literature and performed a pooled analysis combining a prospectively collected cohort of critically ill COVID-19 patients with individual and aggregate patient data from the literature.

**Materials And Methods**

**PANDEMIC registry**

Cases with new ICH documented on computed tomography (CT) or magnetic resonance imaging (MRI) and simultaneous RT-PCR confirmed infection of COVID-19 were extracted from the prospective register study PANDEMIC (Pooled Analysis of Neurologic DisordErs Manifesting in Intensive care of COVID-19), which is conducted by the research network IGNITE (Initiative of German NeuroIntensive Trial Engagement) with support of the German Society for Neurologic Intensive Care and Emergency Medicine (DGNI). The PANDEMIC study aims to systematically elucidate neurologic manifestations in exclusively critically ill COVID-19 patients. Age, gender, stage of disease, use of anticoagulation, ECMO therapy, non-neurological symptoms and neurological symptoms, ICH subtype, time from COVID-19 diagnosis to ICH diagnosis, pertinent laboratory values, modified Rankin Scale (mRS) on discharge and use of palliative care were extracted from a secured database and transferred to the data extraction sheet (Supplemental 2). Particular disease phases of COVID-19 were defined according to the LEOSS registry (Lean European Open Survey for SARS-CoV-2 Infected Patients): 1. uncomplicated phase without symptoms or slight symptoms of upper respiratory tract, fever or diarrhea; 2. complicated phase when patients required...
oxygen supplementation; 3. critical phase involving mechanical ventilation, dialysis and/or catecholamines. (14) Local ethics committees and institutional review boards of the participating centers approved the study based on the central vote of the ethics committee of Landesärztekammer Hessen, Germany (state medical association, 2020-1619-evBO, ethikkommission@laekh.de).

**Systematic review**

Eligibility criteria

Recommendations given by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were applied throughout the review. Methods of the analysis and inclusion criteria were specified in advance and registered on the PROSPERO platform. Eligibility criteria were defined as follows: types of participants: COVID-19 patients; exposure: documented ICH during SARS-CoV2 infection; non-English publications, repeat publications on the same cohort, publications on pediatric patients and publications with no full-text availability were excluded.

Search strategy

Studies were identified by searching the MEDLINE database as well as scanning reference lists of articles. The last search was run on March 5, 2021. For the detailed search strategy, please refer to supplemental data (Supplemental 1). Eligibility assessment was performed independently in an unblinded standardized manner by three authors (MLS; RM and KD). Disagreements between reviewers were resolved by consensus. A data extraction sheet was designed, and the data was extracted accordingly. Information was extracted on number of patients with ICH and COVID-19, overall number of patients at risk, age, sex, COVID-19 disease severity, COVID-19 associated symptoms, neurological symptoms, ICH subtype, anticoagulation, ECMO, time from COVID-19 diagnosis to ICH diagnosis, laboratory features, palliative care and mortality or mRS at discharge.

**Statistical analysis**

First, we performed an analysis and provide descriptive statistics of the individual patient data (IPD) from both, the PANDEMIC registry as well as single case reports in the literature. Regression with modified Ranking Scale (mRS) as the dependent variable was not performed due to incomplete data sets and overall low patient numbers. To describe the characteristics of the complete cohort, we used the two-stage method (15) to combine IPD and aggregate patient data in published larger clinical studies. We classified data sets as IPDs whenever patient-specific data was available and used aggregated data when this was not the case. A pooled analysis using the inverse variance method was performed. If not stated otherwise, values derived from the random effects model were used. Inconsistency of the data was measured using the method proposed by Higgins et al. (16) Here, I² of 0–30% was considered as not important, 30–60% as moderate heterogeneity and 60–100% as substantial heterogeneity. We plotted the effect by the inverse of its standard error (‘funnel plot’) to assess potential bias both visually and formally with Egger’s test. Statistical analysis was performed using Microsoft Office Excel Version 365, SPSS (IBM) and R Studio (metafor package).
Results

Literature screening and article selection

Literature search revealed a total of 217 citations. An additional three publications that met the criteria for inclusion were identified by checking reference lists. After excluding duplicates, 214 hits remained. Of these, 107 did not meet the eligibility criteria after reviewing titles and abstracts, 28 additional studies had to be removed after full text review. Overall, a total of 79 studies were identified for inclusion in the review (Fig. 1). These comprised 26 studies with aggregate level data (minimal patient number n = 3; maximum patient number n = 42) and 53 single case reports or case series with individual level data. Together, data sets of 477 patients were available for analysis (34 individual patient level data sets from the PANDEMIC registry, 108 individual level data sets and 335 aggregate patient level data sets from published reports).

Baseline characteristics of individual level patient data

Overall, a total of 34 patients from the PANDEMIC registry fulfilled the inclusion criteria. The demographic and clinical characteristics of patients from the PANDEMIC registry as well as the results for all individual level patient data (n = 142) are shown in Supplemental 3. Clinical outcome as measured by mRS at discharge (0–2 vs. 3–6) was significantly predicted by critical disease stage (20.0% vs 66.4%, p < 0.001), time from COVID-19 diagnosis to ICH diagnosis (9.5 days vs 16.0 days, p = 0.012), headache (40.0% vs 11.2%, p = 0.012) and palliative care (0% vs 38.6%, p = 0.015) (Supplemental 4).

Pooled analysis of aggregate data

The key results from the two-stage pooled analysis including individual level patient data (n = 142 patients) as well as aggregate level data (n = 335 patients) are displayed in Table 1.

Here, median age was 58.8 years (95% CI 54.8 years-62.9 years; I^2 = 85.6%) and 34.0% patients were female (95% CI 29.5% – 40.4%; I^2 = 0%). 23.3% patients experienced critical stage of COVID-19 (95% CI 8.9% – 61.2%, I^2 = 53.8%). 62.7% were on anticoagulation (95% CI 38.2% – 103.0%, I^2 = 82.6%), and 27.5% received ECMO (95% CI 5.8% – 130.2%, I^2 = 92.7%). Median time from COVID-19 diagnosis to diagnosis of ICH was 21.5 days (95% CI 14.9 days – 28.0 days, I^2 = 92.3%). Most frequently observed clinical symptoms were respiratory symptoms (60.9%, 95% CI 41.2% – 90.0%, I^2 = 64.0%) and altered level of consciousness (57.3%, 95% CI 39.9% – 82.3%, I^2 = 45.0%). Microbleeds (51.1%, 95% CI 31.1% – 84.2%, I^2 = 85.1%), SAH (26.6%, 95% CI 16.8% – 42.0%, I^2 = 61.2%) and IPH (33.7%, 95% CI 23.3% – 48.8%, I^2 = 63.7%) were most frequently documented as ICH subtypes. Laboratory results show elevated CRP (228.1 mg/L; 95% CI 200.1 mg/L – 256.0 mg/L; I^2 = 0%), leukocytosis (13.1×10^9/L, 95% CI 6.6×10^9/L – 19.5×10^9/L, I^2 = 97.4%) with normal platelet count (222.9×10^9/L, 95% CI 193.9×10^9/L – 251.8×10^9/L; I^2 = 63.9%) as well as moderately elevated INR (1.4, 95% CI 1.1–1.6; I^2 = 93.7%). aPTT was 45.5 s (95% CI 34.2 s – 56.7 s; I^2 = 98.3%). Data heterogeneity as described by I^2 is moderate to high in most of the variables.
Twelve studies reported data on the incidence of ICH in COVID19 patients (Fig. 2). Eleven studies reported mortality rates in patients with ICH and COVID19 (Fig. 3). Using the random effects model yielded an incidence of 0.85% (95% CI 0.36%-1.99%; $I^2 = 97.5\%$) and a mortality of 52.18% (95% CI 40.40%-67.39%; $I^2 = 51.7\%$), respectively.

Data heterogeneity turned out high for incidence data ($I^2 = 97\%$) and moderate for mortality data ($I^2 = 59\%$). To further explore this heterogeneity, a funnel plot was drawn. With regard to the data on mortality, the funnel plot appears symmetrical on visual inspection, and Egger's test result is non-significant ($p = 0.80$). However, data on incidence shows pronounced horizontal scatter of effect estimates, with Egger's test being significant for asymmetry ($p = 0.04$) (Fig. 4).

**Discussion**

This systematic review and pooled analysis provides new insights into incidence, mortality and key clinical features of ICH in COVID19 patients.

The calculated incidence for ICH in COVID-19 patients in our study was low (0.85%, 95% CI 0.36%-1.99%; $I^2 = 97.5\%$), but moderately increased in comparison to a large cohort on hemorrhagic stroke in COVID-19 patients (0.3%; data from French national administrative database).(17) More importantly, it was higher than the incidence reported from the 2018–2019 seasonal influenza cohort (0.2%).(17) However, a substantial amount of patients in our report suffered microbleeds, which are not mentioned and might have been missed in the French administrative database. Apart from microbleeds, frequent subtypes of ICH were IPH and SAH. Mortality in our study was 52.18% (95% CI 40.40%-67.39%; $I^2 = 51.7\%$), whereas case-fatality rate for ICH in non-COVID-19 patients is reported at approximately 40%.(18) Case fatality rates for COVID-19 patients requiring invasive mechanical ventilation was found to be 45% in a large meta-analysis. (19) As only our cohort combines both potentially fatal diagnosis (ICH and COVID-19), a higher mortality is reasonable.

On individual patient level, critical disease stage (20.0% vs 66.4%, $p < 0.001$), time from COVID-19 diagnosis to ICH diagnosis (9.5 days vs 16.0 days, $p = 0.012$), headache (40.0% vs 11.2%, $p = 0.012$) and palliative care (0% vs 38.6%, $p = 0.015$) were significant predictors of outcome (mRS 0–2 vs mRS 3–6). Critical stage of COVID-19 and headaches in the context of IPH have been previously described as predictors for worse outcome.(20, 21) In our study, however, headache predicted a better functional outcome (mRS 0–2) at discharge. The discrepancy to already published data may be explained by a bias that could have developed because headache had been coded for both, COVID-19 and ICH. Although bleeding diathesis has been a fundamental factor in ICH in both COVID-19 and non-COVID-19 patients, (22, 23) and a significant proportion of patients had anticoagulation and showed changes in the respective biological biomarkers (aPTT, INR) in this cohort, we did not find anticoagulation to be a significant variable in our study. However, as we were not able to specify whether patients received prophylactic or therapeutic dose anticoagulation from the data provided, the effect on the outcome might be underestimated.
By pooled analysis of aggregate level data, we provided detailed descriptive statistics but refrained from meta-regression due to incomplete data sets and thus insufficient statistical power. Patients with ICH during active COVID-19 were predominantly male with a median age of 58.8 years [95% CI 54.8; 62.9]. Basic epidemiological data are thus comparable to already published cohorts of COVID-19.(21, 24) The majority of patients experienced a critical phase of disease, with respiratory symptoms and altered level of consciousness being the dominant clinical features. The high proportion of patients with critical stage of COVID-19 is consistent with studies reporting a relative increase of neurological symptoms with more severe disease.(2, 25) Median time from COVID-19 diagnosis to diagnosis of ICH was 21.5 days [95% CI 14.9; 28.0], which might be due to diagnostic difficulties in critically ill patients, or due to COVID-19-specific vasculopathy in the subacute stage of disease, or both. The high proportion of patients of receiving ECMO further illustrates severity of disease in this cohort. Yet, with a recent analysis reporting similar rates of IPH in COVID-19 and propensity score matched controls without COVID-19,(26) it appears unlikely that the viral infection is an independent risk factor further aggravating the already existing substantial risk of ICH during ECMO therapy. As ICH has been known to be a fatal complication of ECMO in COVID-19, as well as in other etiologies of acute respiratory distress syndrome (ARDS), cranial imaging should be encouraged in cases with neurological deterioration.(27, 28)

The pathomechanism behind COVID-19’s association with ICH is still highly controversial, and many hypothetical constructs describing both direct and indirect effects of virus infection have been described. (8) With neurotropism having been demonstrated, potential direct mechanisms include infection of vascular endothelium and consecutive endothelitis(7, 29) as well as downregulation of ACE2 leading to elevated levels of angiotensin II with inflammation, increase of blood pressure and other deleterious downstream effects.(30) Hyperinflammatory syndrome with loss of vascular integrity and disseminated coagulation are further described to play a role as indirect mechanisms.(31, 32)

Given that the different subtypes of ICH have a distinct pathophysiology, it appears plausible that the magnitude of the role of SARS-CoV2 described above varies.

First, it is reasonable that in traumatic ICH, such as EDH, SDH or traumatic SAH, concomitant SARS-CoV2 infection is probably not a driving cause.

Second, critical illness-associated cerebral microbleeds are discussed to be a consequence of hypoxemia, uremia and microangiopathy, or a combination of such.(33–37) Cerebral microbleeds are frequently observed in patients with high-altitude cerebral edema(34) and those affected exhibit significant respiratory failure. When compared to patients without microbleeds, respiratory failure is more pronounced.(33, 35–37) Furthermore, such bleeding patterns have also been observed in COVID-19- and non-COVID- acute respiratory distress syndrome (ARDS) patients.(36, 38) The currently available data, however, do not allow to speculate on whether or not this is a specific complication of ECMO or due to hypoxemia during the course ARDS. Furthermore, the formation of microthrombi described in COVID-19 as well as in disseminated intravascular coagulation (DIC) in the context of critical disease might also play a relevant role in the pathogenesis of microbleeds(39, 40). Two studies investigating microbleeds in
COVID-19 suggested a potential role for COVID-19-associated microangiopathy as patients with microbleeds showed thrombocytopenia and elevated D-Dimers. (33, 36) Overall, it is impossible to state whether the observed bleedings are COVID-19-associated rather than a phenomenon caused by critical illness.

Third, the above-mentioned hypercoagulable features may predispose patients for thromboembolic complications in the venous and arterial circulation. However, with regards to ischemic stroke, epidemiological data do not show a higher incidence among COVID-19 patients. (17, 41) Thus, secondary ICH due to hemorrhagic transformation/parenchymal hematoma is likely to be dependent on the use of antithrombotic agents in stroke management rather than direct effects of SARS-CoV2. Sinus venous thrombosis is infrequently reported in the context of COVID-19 but may be driven by its hypercoagulable features. (42) Overall reports included too small patient numbers to deduct a reasonable incidence.

Fourth, only very few cases of SAH during COVID-19 have been described. In aneurysmal SAH, the hypothesis of arterial weakening by viral infection has been eliminated decades ago. Today, there is no additional evidence that SARS-CoV2 could contribute to the pathogenesis of non-traumatic SAH. (43)

As for IPH, a systematic review and pooled analysis revealed 67.7% of patients exhibited atypical, lobar IPH, while in non-COVID-19 cohorts, proportions of 32–38% are reported. Furthermore, COVID-19 patients with ICH had multilocular manifestation of ICH in 20.6%, while others reported a prevalence of only about 6% for more heterogeneous cohorts. In line with those findings of atypical localization, only 53% of patients had arterial hypertension. Overall, this suggests that additional factors may play a role in ICH in COVID-19 patients. As a majority receives anticoagulation and some even receive ECMO, it is likely that, besides the complex mechanisms already described above, those therapeutic interventions play a pivotal role. Indeed, therapeutic anticoagulation was found to increase the risk of IPH in COVID-19 by approximately 5-fold and was found to be a predictor of mortality.

This review has several limitations. First, data sets are incomplete due to a great heterogeneity of variables being reported, with detailed information for the cohort of interest often being unavailable in aggregate level data. Second, and although inherent to any meta-analysis of special significance in this case, there are relevant sources of bias. As the pandemic is highly dynamic and often requires rapid review and publication of scientific results, it is likely that data irregularities due to methodological issues or publication bias are particularly relevant in this research field. On the other hand, the limited resources during the pandemic with potentially limited access to health care facilities could lead to a substantial amount of undetected and underreported cases. Finally, data on an adequate control group has not been available.

**Conclusion**

In this systematic review and pooled analysis, we found intracranial hemorrhage associated with COVID-19 in 0.85% of cases, and to be associated with poor prognosis. Given the potentially devastating consequences of ICH, cranial imaging should be encouraged in cases with neurological deterioration. As
ICH represent a heterogeneous entity, the magnitude of SARS-CoV2-associated effects most likely depends on the ICH subtype. More accurate epidemiological data and further pathophysiological insights are warranted to guide future clinical management.

Table
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Mean [95%-CI]</th>
<th>(i^2) [95%-CI]</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.8 [54.8; 62.9]</td>
<td>85.6% [75.9%; 91.4%]</td>
<td>11</td>
</tr>
<tr>
<td>Female (%)</td>
<td>34.0 [29.5; 40.4]</td>
<td>0.0% [0.0%; 36.0%]</td>
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</tr>
<tr>
<td>Critical disease (%)</td>
<td>23.3 [8.9; 61.2]</td>
<td>53.8% [0.0%; 83.0%]</td>
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</tr>
<tr>
<td>ECMO (%)</td>
<td>27.5 [5.8; 130.2]</td>
<td>92.7% [82.0%; 97.0%]</td>
<td>3</td>
</tr>
<tr>
<td>Anticoagulation (%)</td>
<td>62.7 [38.2; 103.0]</td>
<td>82.6% [55.3%; 93.2%]</td>
<td>4</td>
</tr>
<tr>
<td>Time from COVID-19 diagnosis to ICH diagnosis (days)</td>
<td>21.5 [14.9; 28.0]</td>
<td>92.3% [86.0%; 95.8%]</td>
<td>6</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>36.6 [19.9; 63.5]</td>
<td>71.0% [17.3%; 89.9%]</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory symptoms (%)</td>
<td>60.9 [41.2; 90.0]</td>
<td>64.0% [0.0%; 87.8%]</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia/arthralgia (%)</td>
<td>7.0 [3.8; 13.1]</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Malaise (%)</td>
<td>8.5 [4.8; 14.9]</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurological deficits (%)</td>
<td>23.8 [16.8; 33.8]</td>
<td>16.4% [0.0%; 82.6%]</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1
Pooled analysis of baseline characteristics
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Mean [95%-CI]</th>
<th>$\text{I}^2$ [95%-CI]</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered level of consciousness (%)</td>
<td>57.3 [39.9; 82.3]</td>
<td>45.0% [0.0%; 79.8%]</td>
<td>5</td>
</tr>
<tr>
<td>Encephalopathy (%)</td>
<td>24.4 [7.4; 80.1]</td>
<td>90.5% [78.7%; 95.8%]</td>
<td>4</td>
</tr>
<tr>
<td>Headache (%)</td>
<td>13.9 [8.5; 20.1]</td>
<td>0% [NA]</td>
<td>2</td>
</tr>
<tr>
<td>Anisocoria (%)</td>
<td>20.4 [14.2; 29.4]</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Seizure (%)</td>
<td>8.4 [4.6; 15.4]</td>
<td>21.6% [0.0%; 67.1%]</td>
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<tr>
<td>ICH</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IPH (%)</td>
<td>33.7 [23.2; 48.8]</td>
<td>63.7% [30.6%; 81.0%]</td>
<td>11</td>
</tr>
<tr>
<td>SAH (%)</td>
<td>26.6 [16.8; 42.0]</td>
<td>61.2% [27.2%; 79.3%]</td>
<td>12</td>
</tr>
<tr>
<td>SDH/EDH (%)</td>
<td>12.6 [4.4; 35.9]</td>
<td>84.0% [66.7%; 92.3%]</td>
<td>6</td>
</tr>
<tr>
<td>Microbleeds (%)</td>
<td>51.1 [31.1; 84.2]</td>
<td>85.1% [74.4%; 91.4%]</td>
<td>10</td>
</tr>
<tr>
<td>IVH (%)</td>
<td>5.9 [3.0; 11.6]</td>
<td>2.7% [NA]</td>
<td>2</td>
</tr>
<tr>
<td>HT/PH of IS (%)</td>
<td>9.2 [2.2; 39.1]</td>
<td>80.0% [36.7%; 93.7%]</td>
<td>3</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Mean [95%-CI]</td>
<td>$I^2$ [95%-CI]</td>
<td>Number of studies</td>
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<tr>
<td>---------------------------------------------------------------</td>
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</tr>
<tr>
<td>SVT with hemorrhage (%)</td>
<td>2.9 [1.2; 7.1]</td>
<td>0% [NA]</td>
<td>2</td>
</tr>
<tr>
<td>Other (%)</td>
<td>46.2 [25.2; 84.8]</td>
<td>76.4% [50.3%; 88.7%]</td>
<td>7</td>
</tr>
<tr>
<td>Multilocular ICH, not further specified (%)</td>
<td>23.0 [6.1; 0.87.0]</td>
<td>83.8% [59.0%; 93.6%]</td>
<td>4</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells ($\times 10^9$/L)</td>
<td>13.1 [6.6; 19.5]</td>
<td>97.4% [95.5%; 98.5%]</td>
<td>4</td>
</tr>
<tr>
<td>Platelet count ($\times 10^9$/L)</td>
<td>222.9 [193.9; 251.8]</td>
<td>63.9% [12.7%; 85.1%]</td>
<td>6</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>228.1 [200.1; 256.0]</td>
<td>0% [NA]</td>
<td>2</td>
</tr>
<tr>
<td>INR</td>
<td>1.4 [1.1; 1.6]</td>
<td>93.7% [87.0%; 96.9%]</td>
<td>4</td>
</tr>
<tr>
<td>apTT (sec)</td>
<td>45.5 [34.2; 56.7]</td>
<td>98.3% [97.2%; 98.9%]</td>
<td>4</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td>8.2 [1.8; 14.6]</td>
<td>98.1% [96.5%; 99.0%]</td>
<td>3</td>
</tr>
</tbody>
</table>

Pooled analysis of baseline characteristics including all available aggregate data. Individual data was aggregated prior to this analysis according to the two-stage method and was subsequently counted as one study. The number of total studies included in the analysis is displayed. Means and the 95% confidence interval are derived from the random effects model. Level of heterogeneity was expressed by $I^2$ together with the 95% confidence interval.


**Declarations**

**Ethics approval:**

Local ethics committees and institutional review boards of the participating centers approved the study based on the central vote of the ethics committee of Landesärztekammer Hessen, Germany (state medical association, 2020-1619-evBO, ethikkommission@laekh.de).

**Consent for publication:**

Not applicable

**Availability of data and materials:**

All data generated or analysed during this study are included in this published article [and its supplementary information files].

**Competing interests:**

The authors declare that they have no competing interests.

**Funding:**

No special funding was received.

**Authors’ contributions:**

MLS: conceptualization, methodology, software, data acquisition, formal analysis, data curation, writing manuscript; CF, FS, CK, RM, SK, MW, BM, JB, JG, PL, SL, EHA, KJ, BK, IS, WM, QN, MD, AG, OAO & Jk-B: data acquisition, data curation, revising manuscript; KD & AG: conceptualization, methodology, data acquisition, data curation, revising manuscript.

**Acknowledgements:**
References


Figure 1

Literature screening and selection process. Study selection diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group statement.(44)
Figure 2

Incidence of ICH in COVID-19 patients. Random and fixed effects model for incidence of ICH in COVID-19 patients. Effects estimates were calculated using the inverse variance method and are represented by squares with the size of the square being proportional to the weight assigned to the study in the meta-analysis and the respective 95% confidence intervals. Lines indicate the respective 95% confidence intervals.

Figure 3

Incidence of ICH in COVID-19 patients. Random and fixed effects model for incidence of ICH in COVID-19 patients. Effects estimates were calculated using the inverse variance method and are represented by squares with the size of the square being proportional to the weight assigned to the study in the meta-analysis and the respective 95% confidence intervals. Lines indicate the respective 95% confidence intervals.
Mortality of ICH in COVID-19 patients. Random and fixed effects model for mortality of ICH in COVID-19 patients. Effects estimates were calculated using the inverse variance method and are represented by squares with the size of the square being proportional to the weight assigned to the study in the meta-analysis. Lines indicate the respective 95% confidence intervals.

Figure 4

Heterogeneity and bias of studies reporting incidence and mortality of ICH in COVID-19 patients. Standard error as an indicator of study precision is plotted against study results (A: mortality; B: incidence), with the vertical line representing the value derived from the random effects model. The diagonal lines indicate the corresponding 95% confidence intervals (‘funnel plot’). Each dot represents a single study. Egger’s test for funnel plot asymmetry is significant for mortality (p=0.04), but not for incidence (p=0.80).

Supplementary Files

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