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Imaging features and ultraearly hematoma growth in intracerebral hemorrhage associated with COVID-19

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Abstract

Purpose Intracerebral hemorrhage (ICH) is an uncommon but deadly event in patients with COVID-19 and its imaging features remain poorly characterized. We aimed to describe the clinical and imaging features of COVID-19-associated ICH.

Methods Multicenter, retrospective, case–control analysis comparing ICH in COVID-19 patients (COV19 +) versus controls without COVID-19 (COV19 −). Clinical presentation, laboratory markers, and severity of COVID-19 disease were recorded. Non-contrast computed tomography (NCCT) markers (intrahematoma hypodensity, heterogeneous density, blend sign, irregular shape fluid level), ICH location, and hematoma volume (ABC/2 method) were analyzed. The outcome of interest was ultraearly hematoma growth (uHG) (defined as NCCT baseline ICH volume/onset-to-imaging time), whose predictors were explored with multivariable linear regression.

Results A total of 33 COV19 + patients and 321 COV19 − controls with ICH were included. Demographic characteristics and vascular risk factors were similar in the two groups. Multifocal ICH and NCCT markers were significantly more common in the COV19 + population. uHG was significantly higher among COV19 + patients (median 6.2 mL/h vs 3.1 mL/h, $p = 0.027$), and this finding remained significant after adjustment for confounding factors (systolic blood pressure, antiplatelet and anticoagulant therapy), in linear regression (B(SE) = 0.31 (0.11), $p = 0.005$). This association remained consistent also after the exclusion of patients under anticoagulant treatment (B(SE) = 0.29 (0.13), $p = 0.026$).

Conclusions ICH in COV19 + patients has distinct NCCT imaging features and a higher speed of bleeding. This association is not mediated by antithrombotic therapy and deserves further research to characterize the underlying biological mechanisms.

Keywords Intracerebral hemorrhage · Stroke · COVID-19 · SARS-CoV-2

Introduction

Intracerebral hemorrhage (ICH) is a rare but life-threatening event in patients with SARS-CoV-2 infection [1, 2]. In contrast to ischemic stroke, the clinical and imaging features of COVID-19-associated ICH remain poorly characterized. The radiological characteristics of ICH may provide clues on the pathophysiology and determinants of the disease. In particular, non-contrast computed tomography (NCCT) characteristics such as ICH location, hematoma volume, and presence of NCCT markers of active bleeding might improve the understanding of the biological mechanisms of brain bleeding in patients with COVID-19 [3, 4]. Previous studies showed a high rate of multifocal and lobar bleedings but it remains unclear whether the widespread use of anticoagulation among COVID-19 patients accounts for these findings [5]. We aimed therefore to describe the clinical and neuroradiological NCCT features of COVID-19-associated ICH comparing this group of patients with a cohort of ICH not associated with COVID-19.

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Methods

Patient selection

Retrospective, case–control analysis comparing COVID-19-positive (COV19 +) and negative (COV19 −) patients with acute ICH. COV19 + patients were selected from ten medical centers in Italy (March 2020–May 2021) whereas COV19 − subjects were obtained from two registries enrolling primary spontaneous non-traumatic ICH (2010–2015 and 2017–2019). The same inclusion and exclusion criteria were applied for the selection of the two study populations (COV19 + and COV19 −). We included patients with the following characteristics: (1) primary spontaneous ICH within 24 h from onset/time last seen well, (2) availability of baseline NCCT images, and (3) age > 18. We excluded patients with intracranial bleeding secondary to trauma, vascular malformation, or neoplasm patients who underwent surgery. COV19 + diagnosis was established through PCR detection of SARS-CoV-2 in nasopharyngeal swab.

Clinical variables

Variables of interest included demographics, vascular risk factors, antithrombotic therapy, blood pressure on admission, and Glasgow Coma Scale score. COVID-19 severity was classified based on clinical and radiological presentation as asymptomatic, mild (minor symptoms without pneumonia), moderate (pneumonia), and severe (acute respiratory distress syndrome) [5]. Mortality was assessed at 30 days from the index event screening the national social security database.

Routine admission blood tests, including coagulation tests and platelet count, were available only in COV19 + subjects and were collected within 24 h from ICH onset. ICH management followed the American Stroke Association guidelines [6].

Imaging analysis

NCCT scans were acquired with 3- or 5-mm slice thickness axial reconstruction, according to local protocols at each site. NCCT images were analyzed for determination of ICH volume (ABC/2 method), location (lobar, deep, cerebellum, brainstem, and multifocal), and intraventricular hemorrhage (IVH) presence. In multiple ICH, the total volume was calculated as the sum of the volume of different hemorrhagic foci [7]. Baseline NCCT scans were also analyzed for detection of specific markers of active bleeding (intrahematoma hypodensity, blend sign, fluid level, heterogeneous density, and irregular shape), according to international diagnostic criteria [3]. Imaging raters were blinded to clinical status and outcome. Ultraearly hematoma growth (uHG), a surrogate measure of the bleeding rate, was calculated as baseline hematoma volume divided by onset-to-imaging-time (mL/h) [8], as represented in Fig. 1. An illustrative example of NCCT features is shown in Fig. 2.

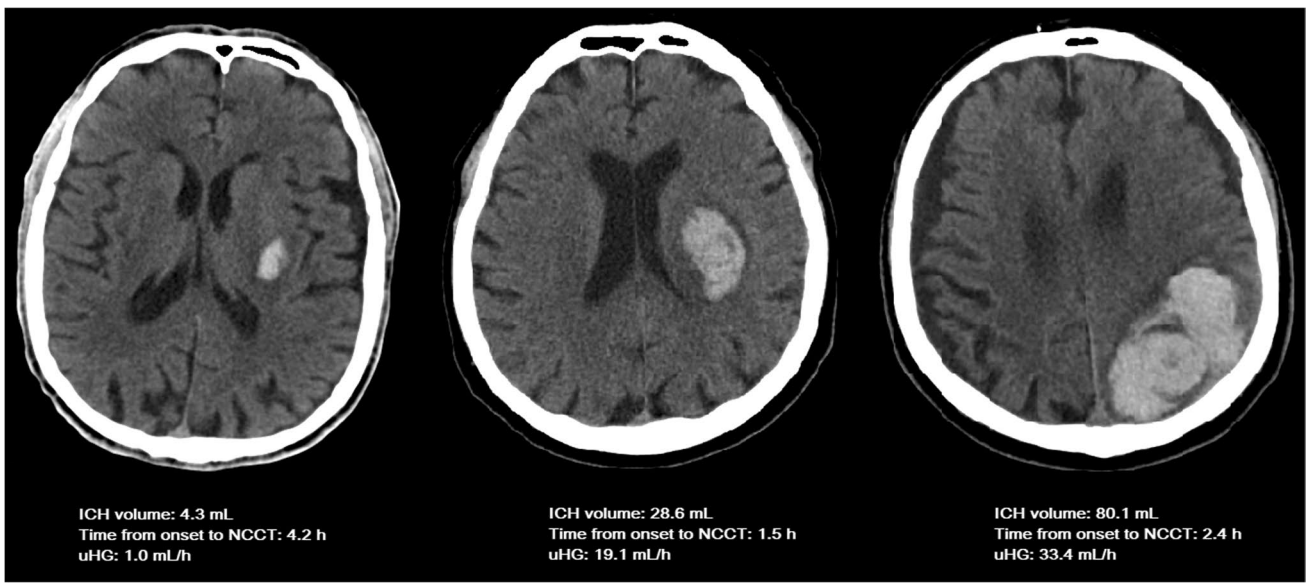

Fig. 1 Ultraearly hematoma growth. Illustrative example of the definition and calculation of ultraearly hematoma growth (baseline ICH volume/time from onset to NCCT). ICH indicates intracerebral hemorrhage; NCCT, non-contrast computed tomography; uHG, ultraerly hematoma growth

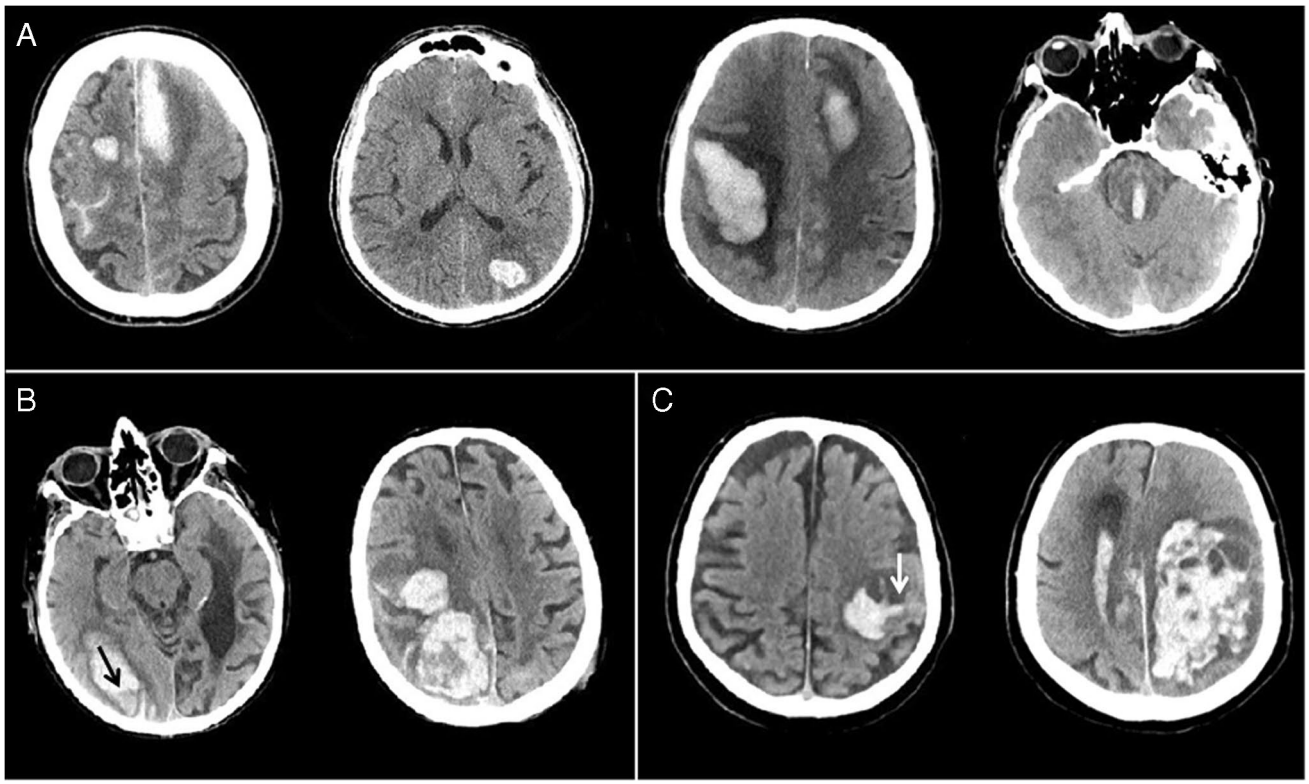

Fig. 2 Imaging features of COVID19-associated ICH. **A** Non-simultaneous multifocal ICHs occurring over 13 days in a patient with asymptomatic COVID-19. **B** Multiple lobar ICHs with evidence of blend sign (black arrow), irregular hematoma shape, and heterogeneous density in a patient with COVID-19 pneumonia. **C** Lobar ICH with fluid level (white arrow) and follow-up NCCT showing significant hematoma expansion and the presence of multiple intrahematoma hypodensities in a patient with COVID-19 pneumonia. ICH, intracerebral hemorrhage; NCCT, non-contrast computed tomography

Statistical analysis

Categorical variables were expressed as percentage and compared with χ^2 test. Continuous variables were expressed as median (interquartile range) or mean (SD) and compared with Mann–Whitney and *t*-test respectively as appropriate. uHG was the main outcome of interest and its predictors were explored with multivariable linear regression (with uHG Log-transformation), adjusting for COV19 status, antiplatelet treatment, anticoagulant treatment, and systolic blood pressure [8, 9]. Unstandardized regression coefficients (*B*) and standard errors (SE) are reported. Two secondary analyses were performed: first, we accounted for multifocal ICH in regression models and, second, patients' anticoagulant-associated cases were excluded. All the analyses were performed with SPSS v 21.0 and statistical significance was set at $p < 0.05$.

Results

We included 33 COV19 + patients and 321 COV19 − controls. Among COV19 + patients, 19 (57.6%) had a diagnosis of COV19 + before ICH onset and 14 (42.4%) were diagnosed during the admission for ICH. Moderate to severe interstitial pneumonia was the most common clinical presentation of COVID-19 ($n = 22$, 66.7%) whereas the remaining 11 (33.3%) had mild or no symptoms. All COV19 + had a platelet count > 50.000/mm3 and normal coagulation tests, except those on anticoagulant therapy.

Table 1 shows the comparison between COV19 + and COV19 − patients. Age and vascular risk factor profile were similar in the two groups and the frequency of oral anticoagulant therapy was not statistically different. COV19 + patients had a higher frequency of heparin therapy before ICH onset and were diagnosed earlier than COV19 − patients (median time from onset to NCCT 2.5 vs 3.8 h, $p = 0.001$). All NCCT markers (hypodensities, irregular shape, heterogeneous density, blend sign, and fluid level) infratentorial and multifocal ICH were more common in COV19 + patients. In particular, the frequency of multifocal ICH was 0.6% in COV19 − patients and 12.1% in COV19 + patients. Baseline ICH volume was similar in the two groups (median 13 vs 16 mL, $p = 0.259$) but uHG was higher in COV19 + patients (6.2 vs 3.1 mL/h, $p = 0.027$). This finding remained significant after adjustment for confounders in linear regression (B (SE) = 0.31 (0.11),

Table 1 Comparison between patients with and without COVID-19

	COVID-19 NEG ($n=321$)	COVID-19 POS ($n=33$)	p
Age, median (IQR), y	70 (63–76)	71 (55–86)	0.441
Sex, male, *n* (%)	168 (52.3)	22 (66.7)	0.116
Hypertension, *n* (%)	201 (62.6)	22 (66.7)	0.646
Diabetes, *n* (%)	61 (19.0)	10 (30.3)	0.123
Antiplatelet treatment, *n* (%)	105 (32.7)	6 (18.2)	0.087
Oral anticoagulant treatment, *n* (%)	29 (9.0)	6 (18.2)	0.094
Heparin treatment			< 0.001
No, *n* (%)	321 (100)	27 (81.8)	
Prophylactic LMWH, *n* (%)	0 (0)	3 (9.1)	
Anticoagulant LMWH, *n* (%)	0 (0)	2 (6.1)	
Unfractioned heparin, *n* (%)	0 (0)	1 (3.0)	
SBP, mean (SD), mmHg	157 (29)	165 (38)	0.134
DBP, mean (SD), mmHg	87 (15)	91 (22)	0.224
GCS, median (IQR)	11 (9–14)	13 (7–15)	0.591
Baseline NCCT timing, median (IQR), h	3.8 (2.6–6.7)	2.5 (2.0–4.0)	0.001
Baseline ICH volume, median (IQR), mL	13 (6–30)	16 (8–52)	0.259
Ultraearly hematoma growth, median (IQR), mL/h	3.1 (1.3–6.1)	6.2 (1.9–25.9)	0.027
ICH location			< 0.001
Deep, *n* (%)	189 (58.9)	15 (45.5)	
Lobar, *n* (%)	127 (39.6)	7 (21.2)	
Cerebellar, *n* (%)	2 (0.6)	4 (12.1)	
Brainstem, *n* (%)	1 (0.3)	3 (9.1)	
Multifocal, *n* (%)	2 (0.6)	4 (12.1)	
Presence of IVH, *n* (%)	76 (23.7)	10 (30.3)	0.398
Hypodensities, *n* (%)	116 (36.1)	27 (81.8)	< 0.001
Heterogeneous density, *n* (%)	116 (36.1)	20 (60.6)	0.006
Blend sign, *n* (%)	50 (15.6)	15 (45.5)	< 0.001
Irregular shape, *n* (%)	153 (47.7)	22 (66.7)	0.038
Fluid level, *n* (%)	14 (4.4)	5 (15.2)	0.009
Mortality at 30 days, *n* (%)	33 (10.3)	16 (48.5)	< 0.001

IQR, interquartile range; *LMWH*, low molecular weight heparin; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *SD*, standard deviation; *NCCT*, non-contrast computed tomography; *GCS*, Glasgow coma scale; *ICH*, intracerebral hemorrhage; *IVH*, intraventricular hemorrhage

$p=0.005$). Additional analyses accounting for multifocal ICH and excluding subjects on any anticoagulant treatment confirmed the association between COV19 + and higher uHG (B (SE) = 0.24 (0.12), $p=0.037$ and B (SE) = 0.29 (0.13), $p=0.026$ respectively). Mortality at 30 days was significantly higher in COV19 + patients (48.5% vs 10.3%, $p<0.001$).

Discussion

This retrospective analysis comparing COV19 + and COV19 − patients with ICH showed that COVID-19-associated ICH had specific imaging features. In particular, we observed a higher speed of bleeding, and a higher prevalence of multifocal ICH and NCCT markers in COV19 + patients, independently from vascular risk factor profile.

Our findings are best interpreted as hypothesis generating and suggest the presence of different biological mechanisms in COV19 + and COV19 − patients with acute ICH.

A higher frequency of multifocal hemorrhages and a higher extent of bleeding have been previously reported in anticoagulant-associated ICH and therefore anticoagulant treatment may account for these observations [7]. However, our findings do not support this hypothesis as the association between COV19 + and uHG remained significant after the inclusion of anticoagulation in linear regression and also in secondary analyses excluding anticoagulant-associated ICH patients. Several other mechanisms may explain our observations. Endothelial

injury is a key event in the natural history of COVID-19 infection and the presence of multifocal endothelial damage to cerebral small vessels may explain the presence of multiple sites of bleeding and the faster bleeding pace in COV19 + patients [10]. Impaired hemostasis may also account for our findings, arising from severe systemic inflammation with massive cytokine release [11]. Impaired clotting might also be the consequence of consumption coagulopathy due to hyperactivation of the fibrinolytic system [11]. These speculations are indirectly supported by the imaging pattern observed in COV19 + patients in our population. In particular, NCCT markers represent foci of less mature and unstable blood with active bleeding [3] and all these imaging markers were more common in the COV19 + cohort. Likewise, multifocal ICH is frequently observed in patients with coagulopathy and was significantly more prevalent in the COV19 + group, also after the exclusion of anticoagulant-associated cases. Although we observed normal coagulation tests in non-anticoagulated patients with ICH and COV19 + , it is possible that a subtle coagulation impairment is not detected by routine blood tests.

Some limitations of our work should be acknowledged. First, intracranial vessel imaging was not standardized and performed in many included patients. Signs of intracranial vessel wall inflammation have been recently described in COV19 + patients with neurological involvement and we were not able to systematically investigate this potential determinant of intracranial bleeding [12, 13]. Second, selection bias in favor of less severely affected patients may have occurred, as all the included subjects were not primarily admitted to intensive care or neurosurgery units. Third, ABC/2 method for ICH volume determination may be less accurate compared to planimetric software. Fourth, routine blood tests were not available in the control population of COV19 − subjects. Finally, the presence of an association does not necessarily imply causality and our findings require confirmation.

Conclusion

ICH in COV19 + patients has distinct neuroimaging features that differ from those observed in ICH not associated with COVID-19. The high frequency of multifocal ICH and NCCT markers of active bleeding suggests the presence of specific biological determinants in COV19 + ICH. Antithrombotic therapy and vascular risk factors did not account for these peculiar imaging features and further research is needed to confirm our findings and characterize the underlying pathophysiology.

Author contribution Andrea Morotti: study concept, statistical analysis, manuscript drafting
Andrea Pilotto: data acquisition, critical revision of the manuscript
Valentina Mazzoleni: data acquisition, imaging analysis, critical revision of the manuscript
Enrico Fainardi: data acquisition, critical revision of the manuscript
Ilaria Casetta: data acquisition, imaging analysis, critical revision of the manuscript
Anna Cavallini: data acquisition, critical revision of the manuscript
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Stefano Gipponi: data acquisition, critical revision of the manuscript
Alessandro Padovani: data acquisition, critical revision of the manuscript, study supervision

Data availability Requests to access the dataset may be sent to the corresponding author.

Declarations

Conflict of interest All the authors report no disclosures.

Ethical approval All the study procedures were approved by the ethics standards committee on human experimentation at the coordinating site (local ethics committee of the ASST Spedali Civili Hospital, Brescia: NP 4067, approved 08.05.2020) and at each participating site. Written informed consent was obtained whenever possible or waived by the ethics standard committee.

Informed consent Informed consent was obtained from all individual participants included in the study or waived by the Ethical Committee.

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