Intracerebral hemorrhage in COVID-19 patients with pulmonary failure – a propensity score matched registry study

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Research Article

Keywords: intracerebral hemorrhage, ARDS, COVID-19

Posted Date: August 11th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-56258/v1>

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Version of Record: A version of this preprint was published at Neurocritical Care on February 23rd, 2021.
See the published version at <https://doi.org/10.1007/s12028-021-01202-7>.

Abstract

Background: Hypercoagulopathy in coronavirus disease 2019 (COVID-19) causing deep vein thrombosis and pulmonary artery embolism necessitate systemic anticoagulation. Case reports of intracerebral hemorrhages in ventilated COVID-19 patients warrant precaution. It is unclear however, if COVID-19 patients with acute respiratory distress syndrome (ARDS) with and without extracorporeal membrane oxygenation therapy (ECMO) have more intracerebral hemorrhages (ICH) compared to other ARDS patients.

Methods: We conducted a retrospective observational single center study enrolling all patients with ARDS from 01/2018-05/2020. Patients with ARDS positive for SARS-CoV2 PCR were allocated to the COVID-19 group. Propensity score matching was performed for age, ECMO and risk of bleeding according to HAS-BLED score.

Results: A total of 163, mostly severe ARDS patients were identified, 116 (71.2%) without COVID-19 and 47 (28.8%) positive for SARS-CoV-2. The two groups were comparable concerning the main confounders of ICH including age, HAS-BLED score, need for ECMO-therapy as well as anticoagulation levels reported. In 63/163 cases (38.7%), veno-venous ECMO therapy was required and ICU survival was 52.8%. Although HAS-BLED-score on admission was generally low (1.6 ± 1.3), intracerebral hemorrhage was detected in 22 patients (13.5%) with no statistical difference between the groups (11.2 vs. 19.1% with and without SARS-CoV-2, respectively, $p=0.21$). Propensity score matching confirmed similar intracerebral bleeding rates in both groups (12.8 vs. 19.1% with and without SARS-CoV-2, respectively, $p=0.57$).

Conclusions: Intracerebral hemorrhage was detectable in every tenth patient with ARDS. We found no statistically significant increased bleeding rate in patients with ARDS due to COVID-19 compared to other causes of ARDS.

Introduction

Several studies point out a state of hypercoagulability occurring in coronavirus disease 2019 (COVID-19) probably due to inflammatory changes comparable to disseminated intravascular coagulopathy.(1,2) Additionally, clinical and pathohistological reports about micro- and macrothrombosis as typical complications in critically ill COVID-19 patients emphasize the need for adjusted thromboprophylaxis treatment.(3–5) Until today, there is no concrete evidence to manage thromboprophylaxis beyond standard indications.(6,7) Ongoing studies focus on more aggressive anticoagulation in order to avoid thromboembolic complications (clinicaltrials.gov last accessed 06/17/2020; 23 trials prophylactic, intermediate, therapeutic heparin doses). Nevertheless, higher anticoagulation targets are already proposed by some clinicians.(8)

Whereas pulmonary embolism, and deep vein thrombosis have been documented frequently in hospitalized COVID-19 patients (3), major bleedings have not been reported on a large scale in these

cohorts even though there seems to be a higher event rate of cerebral events.(9) By now, three cases have been reported with massive intracerebral hemorrhage.(10,11)

During the treatment of our cohort of critical ill COVID-19 patients, three fatal intracerebral hemorrhages occurred. We therefore raised the question if intracerebral hemorrhage is more common in critically ill COVID-19 patients with respiratory failure compared to the general population of patients with acute respiratory distress syndrome (ARDS).

Methods

Patient selection

Consecutively, patients with ARDS (ICD-10 code J80.01; J80.02; J80.03; J80.03; J80.09) were extracted from the hospital data system from 01/01/2018-05/31/2020 and followed until 06/13/2020 and included in our retrospective observational study performed at the University hospital of Freiburg, Germany. For the COVID-19 group critically ill patients with PCR-confirmed SARS-CoV-2 infection and severe respiratory failure were enrolled from 03/2020-05/2020 (first admission 03/08/2020) and followed until 06/13/2020 (COVID-19). The study protocol was approved by the local ethics committee (Ethik-Kommission der Albert-Ludwigs-Universität Freiburg im Breisgau, file number 333/20).

Data collection and statistics

Clinical data reported in this study was collected from our hospital data system and from documentation of transferring hospitals and included: age, sex, sepsis-related organ failure assessment score (SOFA), length of stay, intensive care unit (ICU) survival, invasive mechanical ventilation (IMV) and extracorporeal therapies (renal replacement therapy, RRT and extracorporeal membrane oxygenation, ECMO). ARDS was classified according to the Berlin classification.(12) If ECMO was necessary, ARDS was considered "severe", since calculation of the Horovitz index required for the Berlin classification is not valid in ECMO. To evaluate the overall bleeding risk, we assessed the HAS-BLED score (a well validated score for bleeding risk in chronic atrial fibrillation as well as in acute disease) on admission and 48 hours prior to bleeding.(13,14) Values of non-COVID-19 patients and COVID-19 patients were compared with chi-square test and t-test. Propensity score matching (1:1) was performed between the two groups matched for age, ECMO and the HAS-BLED score using SPSS (version 26, IBM, NYC, USA) and the optimal matching algorithm with a caliper of 0.1. Results were considered as statistically significant when p-value was below 0.05. Graphs were made using Prism, version 8 (GraphPad, San Diego, USA).

Patient management

Patients were transferred from the emergency department, from internal wards or from primary and secondary treatment centers. Our center is a tertiary treatment center with a high percentage of hospital transfers for ECMO evaluation or after ECMO pick up. All patients received guideline-conform ARDS treatment confirmed in house-internal standard operating procedures for lung-protective ventilation,

therapeutic positioning maneuvers as proning and further supportive therapies according to the underlying cause of the disease.(7,15) Anticoagulation strategies followed house-intern standard operating procedures and current guidelines. Since 04/03/2020 COVID-19 patients on ECMO were managed with a coagulation target of partial thromboplastin time (aPTT) at 50-70s. In case of thrombotic events under unfractionated heparin a timely switch to argatroban was performed in these patients; unfractionated heparin being the standard medication for thromboprophylaxis and therapeutic anticoagulation. Non-COVID-19 ECMO patients were managed with a coagulation target of aPTT at 40-50s.

Intracerebral hemorrhage

Cerebral imaging was indicated according to clinical judgment and enlisted for analysis if dated during ICU therapy or shortly after. An experienced radiologist and neurologist re-read all cerebral computed tomography (cCT) scans and cerebral magnet tomography scans image-by-image according to occurrence of intracerebral hemorrhage and pathogenesis. Additionally, new ischemic events were detected and classified according to their pathogenesis; preexisting microangiopathy according the Fazekas classification was looked at.(16) The evaluation of the Fazekas classification was not performed in case of massive cerebral edema or massive intracerebral bleeding.

Results

Baseline characteristics

From January 2018 to May 2020, 163 ARDS patients were identified and included into the analysis. The 116 non-COVID-19 patients presented with ARDS due to an infection in 70%; other etiologies are given in the electronic supplemental material (ESM) table S4. Since March 2020, we included 47 critically ill COVID-19 patients with intensive care therapy due to pulmonary failure (Table 1, Figure 1). On average, patients were aged 60 ± 15 (24-92) years. There were more female patients in the non-COVID-19 group (42.4% vs. 19.1% in non-COVID-19 vs. COVID-19, respectively $p=0.005$) and the SOFA score was higher (11 ± 4 vs 9 ± 4 in non-COVID-19 vs. COVID-19, respectively, $p=0.006$).

A total of 63/163 (38.7%) patients underwent ECMO therapy without difference between the groups. Furthermore, length of ICU stay, days on IMV and days on ECMO did not differ between the two groups. ICU survival was 52.8% and not different between the groups (52.6% vs. 53.2%), mode of death is given in the ESM (Table S3).

Intracerebral hemorrhage

Out of 163 patients, 96 (58.3%) had a cerebral scan (Table 3). The rate of cerebral imaging did no differ between the two groups (60.3% vs 55.3%; non-COVID-19 vs COVID-19). In the non-COVID-19 group, we detected 13 intracerebral hemorrhages compared to 9 in the COVID-19 group (see figure 2). No significant

difference was found between the two groups according to the occurrence of any intracerebral hemorrhage or a fatal intracerebral hemorrhage (Figure 3, ESM Table S3).

The rate of atypical bleedings was numerically higher in the non-COVID-19 group (7/13 vs. 2/9, $p=0.203$) not reaching statistical significance. Multiple intracerebral hemorrhage however were only detected in the COVID-19 group (0/13 vs. 4/9, $p=0.017$). After propensity score matching, results could be confirmed with similar rates of intracerebral hemorrhage in patients without and with COVID-19 (Figure 3). No difference was detectable in new strokes (12.9% vs. 6.4% for non-COVID-19 and COVID-19 group, respectively) with a high rate of embolic origin (77.8%) and no proximal vessel occlusions.

Risk factors for bleeding and anticoagulation

On admission, patients presented with a low HAS-BLED score 1.6 ± 1.3 (0-4) similar between the two groups (Table 2). The HAS-BLED score 48 hours prior to intracerebral hemorrhage was similar in non-COVID-19 and COVID-19 patients. Alcohol abuse (a risk factor in the HAS-BLED score) was detected significantly more often in the non-COVID-19 patients ($p=0.007$).

Anticoagulation targets for individual patients did not differ during the ICU stay with a higher tendency to reach a therapeutic aPTT in COVID-19 patients (33.6% vs. 44.7%; non-COVID-19 vs COVID-19). Laboratory tests were similar between the groups concerning platelet count, INR and aPTT (Table S2).

Unfractionated heparin was used significantly more often in non-COVID-19 patients ($p=0.01$); whereas more COVID-19 patients were switched to argatroban ($p<0.001$). Blood pressure excess or aPTT excess 48 hours prior to the intracerebral hemorrhage were rare. The Fazekas score between the groups was similar (1.3 ± 0.9 vs 1.0 ± 0.8 ; non-COVID-19 vs COVID-19, $p=0.293$).

Discussion

Intracerebral hemorrhages and ARDS

We found an intracerebral hemorrhage in 13.5% of all ARDS patients with a tendency towards higher bleeding rate in COVID-19 patients not reaching statistical significance neither in the whole cohort nor after propensity score matching. To our best knowledge, this is the first study elucidating the risk of intracerebral hemorrhages in COVID-19. So far, only case reports of devastating intracerebral hemorrhages have been published.(10,11)

We can only speculate why the rate of intracerebral hemorrhages is so high in the ARDS collective. For SARS-CoV2, neuroinvasion and neurotropism have been reported and the Coronavirus was isolated from cerebrospinal fluid and brain tissue.(17,18) In a systematic review, long-term cognitive impairment in a collective of mixed ARDS patients was detected in 70-100% patients at hospital discharge and in 20% 5 years after the ARDS.(19) An imaging study revealed cerebral and hippocampal atrophy one year after ARDS compared to healthy controls.(20) Since the rate of intracerebral hemorrhage in our study detected in COVID-19 seems comparable to other ARDS, a more general pathomechanism with cerebral damage

due to systemic inflammation might be responsible. Due to the retrospective nature of our study, we cannot determine if intracerebral hemorrhage in ARDS is caused by an embolic event with secondary hemorrhage or if bleedings are caused primarily by neurotropism and local endothelitis.

The observed rate of intracerebral hemorrhages during veno-venous ECMO (20.1%; 13/63) therapy matches the rate reported by Fletcher-Sandersjö et al. 20% (65/351 patients) investigating intracranial hemorrhages during mixed adult ECMO therapy. A systematic literature review suggested incidence of intracranial hemorrhage between 1.8-21% during veno-venous or veno-arterial ECMO. (21,22) ICU survival in our cohort (52.8%) is lower than reported by other data for severe ARDS (38%).(23) Our registry contains severely ill patients as suggested by the predicted mortality of 50.0% according to the SOFA score (24), which might explain these differences.

Anticoagulation during ARDS

In our registry, 60.1% of all ARDS patients were on anticoagulation other than for prophylaxis of deep vein thrombosis. This might partly explain the high incidence of intracerebral bleeding reported. On the other hand, some phenotypes of pulmonary failure proceed with a hyperinflammatory immune answer, circulatory and subsequent multi-organ failure. The underlying coagulopathy results in clinical complications such as deep vein thrombosis, pulmonary artery thrombosis or clotting on extracorporeal organ replacement therapies. Laboratory measures result in elevated d-dimers, prolonged prothrombin time and thrombocytopenia along with elevated markers for inflammation (c-reactive protein, interleucine 6, ferritin).(25–27) A local reaction such as a virus associated endothelitis or a systemic inflammation might also trigger these prothrombotic events.(2,28)

Limitations:

We have to point out several limitations of our study. First, the results of our study are limited in consideration of the small patient numbers. Second, as tertiary treatment center our patients were selected with moderate and severe ARDS as well as high SOFA scores. Results might be different in first and secondary treatment centers. Third, CCT scans were indicated by clinical judgement. It remains unclear how many clinically silent events did occur. Fourth, our anticoagulation regimes under ECMO therapy are empiric for COVID-19 and non-COVID-19 patients and tended to be more aggressive for COVID-19 patients. Fifth, more male patients were in the non-COVID-19 group with male gender being a known factor for intracerebral hemorrhage.(29) In our cohort, we did detect similar bleeding rates in females and males with a tendency towards more bleeding in female patients (19.0% vs 10.5% for females and males, respectively, $p=0.153$). Finally, the rate of intracerebral hemorrhage in our cohort with 13.5% (22/163) and the rate for strokes of 11.0% (18/163) might not be representative for cohorts in primary and secondary treatment centers with lower SOFA scores and lower rates of organ replacement therapies.

Conclusions

Intracerebral hemorrhage was detectable in every tenth patient with ARDS. We found no statistical significant increase in bleeding rate in patients with ARDS due to COVID-19 compared to other causes of ARDS. These data should prompt future trials.

Abbreviations

aPTT, partial thromboplastin time

ARDS, severe acute respiratory distress syndrome

BMI, body mass index

cCT, cerebral computed tomography

COVID-19, coronavirus disease 2019

ESM, electronic supplemental material

ER, emergency room

ECMO, extracorporeal membrane oxygenation

ICU, intensive care unit

ICH, intracerebral hemorrhage

IMV, invasive mechanical ventilation

HAS-BLED Score, validated score for bleeding risk in chronic atrial fibrillation as well as in acute disease

RRT, renal replacement therapy

SOFA Score, sepsis-related organ failure assessment score

SARS-CoV-2, severe acute respiratory coronavirus 2

PEEP, positive end-expiratory pressure

Declarations

Ethics approval and consent to participate: The local ethics committee approved the study protocol (Ethik-Kommission der Albert-Ludwigs-Universität Freiburg im Breisgau, file number 333/20).

Consent for publication: According to the local ethics committee according to the retrospective character of the study written or verbal consent was not necessary.

Availability of data and materials: The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Conflict of interests: The authors do hereby declare no conflict of interests.

Permissions information: The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Funding: None.

Authors' contributions: **CNL** conceived and designed the study, performed data acquisition, analysis and interpretation of the data, drafted and revised the manuscript. **JSD** performed data acquisition and interpretation of the data, revised the manuscript. **MBH** performed interpretation of the data, revised the manuscript. **SU** performed interpretation of the data, revised the manuscript. **XB** performed data acquisition and interpretation of the data, revised the manuscript. **VZ** performed interpretation of the data, revised the manuscript. **BS** performed interpretation of the data, revised the manuscript. **PMB** performed interpretation of the data, revised the manuscript. **CB** performed interpretation of the data, revised the manuscript. **KMP** performed interpretation of the data, performed interpretation of the CCT scans, revised the manuscript. **DD** performed interpretation of the data, revised the manuscript. **TW** performed interpretation of the data, revised the manuscript. **WDN** conceived and designed the study, performed interpretation of the CCT scans and data, revised the manuscript. **DLS** conceived and designed the study, created the artwork, performed data analysis and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements: We thank Michaela Kirchenmayer for the collection of extern documentation.

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Tables

Table 1: baseline characteristics of non-COVID-19 patients and COVID-19 patients

	non-COVID-19	COVID-19	all patients
Number of patients	116 (71.2%)	47 (28.8%)	163 (100%)
Age [years]	58±15 (24-83)	66±13 (31-92)	60±15 (24-92)
Female gender	49 (42.2%)	9 (19.1%)	58 (35.6%)
Body mass index [kg/m ²]	30±11 (16-83)	28±6 (18-51)	30±10 (16-83)
Adipositas [BMI≥30 kg/m ²]	32 (33.0%)	13 (28.9%)	45 (31.5%)
Length of stay [days]	18±16 (1-76)	23±20 (1-89)	19±17 (1-89)
SOFA Score	11±4 (2-19)	9±4 (2-17)	10±4 (2-19)
ICU survival	61 (52.6%)	25 (53.2%)	86 (52.8%)
ARDS			
Mild	0	0	0
Moderate	35 (30.2%)	18 (38.3%)	53 (32.5%)
Severe	81 (69.8%)	29 (61.7%)	110 (67.5%)
paO ₂ /FiO ₂ (on day 1)	110±39 (36-222)	113±38 (35-227)	111±38 (35-227)
Highest PEEP (on day 1)	13±4 (5-20)	12±4 (5-19)	12±4 (5-20)
Representative FiO₂ at highest PEEP (on day 1)	58±17 (30-100)	65±19 (40-100)	60±18 (30-100)
Invasive mechanical ventilation (IMV)	106 (91.4%)	40 (85.1%)	146 (89.6%)
Duration of IMV [days]	19±20 (1-129)	23±22 (1-89)	20±21 (1-129)
Renal replacement therapy (RRT)	29 (25.0%)	13 (27.7%)	42 (25.8%)
Extracorporeal membrane oxygenation (ECMO)	49 (42.2%)	14 (29.8%)	63 (38.7%)
Duration of ECMO [days]	16±17 (2-72)	22±20 (2-71)	17±18 (2-72)

Baseline characteristics are displayed for all patients, in non-COVID-19-ARDS and patients with COVID-19-ARDS. Data are n (%) or mean with standard deviation and range. If values differ significantly between non-COVID and COVID-patients, they are marked bold: female: p=0.005; SOFA score: p=0.006; representative FiO₂: p=0.023.

Table 2: risk factors for bleeding

	non-COVID-19	COVID-19	all patients
Number of patients	116 (71.2%)	47 (28.8%)	163 (100%)
HAS-BLED score (on admission)	1.5±1.3 (0-4)	1.7±1.3 (0-4)	1.6±1.3 (0-4)
Hypertension	48 (41.4%)	26 (55.3%)	74 (45.4%)
Abnormal liver function	15 (15.5%)	0	15 (9.2%)
Abnormal kidney function	18 (15.5%)	9 (19.1%)	27 (16.6%)
Former stroke	1 (0.9%)	2 (4.3%)	3 (1.8%)
Former tendency to bleed	2 (1.7%)	0	2 (1.2%)
Unstable INR values	0	0	0
Age >65 years	45 (38.8%)	26 (55.3%)	71 (43.6%)
Blood thinner	30 (25.9%)	17 (36.2%)	47 (28.8%)
Alcohol abuse	16 (13.8%)	0	16 (9.8%)
Coagulopathy prior to ICU	2 (1.7%)	0	2 (1.2%)
Indication for oral anticoagulation prior to ICU	24 (20.7%)	9 (19.1%)	33 (20.2%)
Any oral anticoagulation ^a	20 (17.2%)	10 (21.3%)	30 (18.4%)
Aspirin	13 (11.2%)	9 (19.1%)	22 (13.5%)
Any platelet therapy	16 (13.8%)	13 (27.7%)	29 (17.8%)
Any dual platelet therapy	3 (2.6%)	3 (6.4%)	6 (3.7%)
aPTT target			
<40s (thromboprophylaxis)	51 (44.0%)	14 (29.8%)	65 (39.9%)
40-50s	19 (16.4%)	4 (8.5%)	23 (14.1%)
50-70s	7 (6.0%)	8 (17.0%)	15 (9.2%)
60-80s (therapeutic)	39 (33.6%)	21 (44.7%)	60 (36.8%)
Unfractionated heparin	115 (99.1%)	43 (91.5%)	158 (96.9%)
Argatroban	7 (6.0%)	12 (25.5%)	19 (11.7%)

Risk factors for bleeding are displayed for all patients, in non-COVID-19-ARDS and patients with COVID-19-ARDS. Data are n (%) or mean with standard deviation and range. ^a One patient received fibrinolysis and was not included in this group. ^b 158/163 UFH, 18 were switched to argatroban, 1 patient directly received argatroban. 4 patients received only LMWH. If values are significantly different between non-COVID-19 and COVID-19-patients, they are marked bold: any platelet therapy: p=0.023, alcohol abuse: p=0.007, UFH: p=0.01, argatroban: p<0.001

Table 3: characteristics of intracerebral hemorrhage

	non-COVID-19	COVID-19	all patients
Number of patients	116 (71.2%)	47 (28.8%)	163 (100%)
Cerebral imaging ^a performed	70 (60.3%)	26 (55.3%)	96 (58.3%)
Intracerebral hemorrhage (ICH) detected	13 (11.2%)	9 (19.1%)	22 (13.5%)
Fatal intracerebral hemorrhage	3 (2.5%)	3 (6.3%)	6 (3.7%)
Characteristics of intracerebral hemorrhage			
Typical	1 (7.7%)	0	1 (4.5%)
Atypical	7 (61.5%)	2 (22.2%)	9 (40.9%)
Multiple	0	4 (44.4%)	4 (18.2%)
SAB	3 (23.1%)	2 (22.2%)	5 (22.7%)
SDH/EDH	2 (15.4%)	1 (11.1%)	3 (13.6%)
Intraventricular hemorrhage	4 (30.7%)	2 (22.2%)	6 (27.3%)
RASS on day of hemorrhage	-3.4±1.6 (-5-0)	-3.1±2.2 (-5-0)	-3.2±1.8 (-5-0)
Length of stay until hemorrhage	15.5±19.6 (0-63)	20.4±14.8 (2-47)	17.6±17.6 (0-63)
Hemorrhage during IMV ^b	12 (92.3%)	7 (77.8%)	19 (86.4%)
Hemorrhage during RRT	5 (38.5%)	3 (33.3%)	8 (36.4%)
Hemorrhage during ECMO	9 (69.2%)	4 (44.4%) ^c	13 (50.0%)
HAS-BLED Score 48h prior to hemorrhage	2.3±1.3 (0-4)	2.3±1.4 (0-4)	2.3±1.3 (0-4)
Blood pressure excession 48h prior to hemorrhage	3 (23.1%)	2 (22.2%)	5 (27.3%)
aPTT excess 48h prior to hemorrhage	3 (23.1%)	1 (11.1%)	4 (18.0%)

Characteristics of intracerebral hemorrhage are displayed for all patients, in non-COVID-19-ARDS and patients with COVID-19-ARDS. Data are n (%) or mean with standard deviation and range. ^a 93 cerebral computed tomographies (cCT) only, 2 cerebral magnet resonance tomograophies (cMR) only, 6 cCT and cMR. ^b no ICH under non-invasive ventilation or nasal high flow. ^c in one patient ICH was detected after ECMO weaning but associated with ECMO-therapy and included in this group. If values are significantly different between non-COVID-19 and COVID-19-patients, they are marked bold: multiple ICH p=0.0172.

Figures

Figure 1

Patient flow chart Flow chart of patients in registry. Abbreviations: ARDS acute respiratory distress syndrome, ICH intracerebral hemorrhage

Figure 2

Computed tomographies of three COVID-19 intracerebral hemorrhages. The computed tomographies show three cases of fatal intracerebral hemorrhages in COVID-19 patients with severe pulmonary failure. Case 1: 60-year old female obese health-care worker undergoing steroid therapy due to fibromyalgia. SARS-CoV2 pneumonia resulted in severe ARDS on ECMO and RRT. On day 19 of her clinical course and day 10 after ECMO implantation, she presented with anisocoric pupils. The intracerebral hemorrhage was judged fatal. Case 2: 49-year old otherwise healthy male with severe ARDS on ECMO after SARS-CoV2 transmission presumably at his family doctor's practice. On day 7 after hospitalization and on day 3 after ECMO implantation a fatal intraparenchymatous hemorrhage occurred. Liquor remained negative in the virological testing according to SARS-CoV2. Case 3: 69-year old male with a coronary artery disease and atrial fibrillation with COVID-19 ARDS. On day 9, he presented with anisocoric pupils and the cCT revealed a right frontal cerebral bleeding. Evacuation of the bleeding was performed but the patient deceased. Neuropathology work-up showed a fresh parenchymal and subarachnoidal bleeding and reactive gliotic tissue.

Figure 3

Intracerebral hemorrhage in acute respiratory distress syndrome There was no significant difference between patients with and without COVID-19 in respect to intracerebral hemorrhage as diagnosed by cerebral computed tomography (cCT).

Supplementary Files

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- [TableS1.png](#)
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