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SARS-CoV-2 infection might be a predictor of mortality in intracerebral hemorrhage

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ABSTRACT

Background: SARS-CoV-2 infection may be associated with uncommon complications such as intracerebral hemorrhage (ICH), with a high mortality rate. We compared a series of hospitalized ICH cases infected with SARS-CoV-2 with a non-SARS-CoV-2 infected control group and evaluated if the SARS-CoV-2 infection is a predictor of mortality in ICH patients.

Methods: In a multinational retrospective study, 63 cases of ICH in SARS-CoV-2 infected patients admitted to 13 tertiary centers from the beginning of the pandemic were collected. We compared the clinical and radiological characteristics and in-hospital mortality of these patients with a control group of non-SARS-CoV-2 infected ICH patients of a previous cohort from the country where the majority of cases were recruited.

Results: Among 63 ICH patients with SARS-CoV-2 infection, 23 (36.5%) were women. Compared to the non-SARS-CoV-2 infected control group, in SARS-CoV-2 infected patients, ICH occurred at a younger age (61.4 ± 18.1 years versus 66.8 ± 16.2 years, $P = 0.044$). These patients had higher median ICH scores ([3 (IQR 2–4)] versus [2 (IQR 1–3)], $P = 0.025$), a more frequent history of diabetes (34% versus 16%, $P = 0.007$), and lower platelet counts ($177.8 \pm 77.8 \times 10^9$/L versus $240.5 \pm 79.3 \times 10^9$/L, $P < 0.001$). The in-hospital mortality was not significantly different between cases and controls (65% versus 62%, $P = 0.658$) in univariate analysis;

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however, SARS-CoV-2 infection was significantly associated with in-hospital mortality (aOR = 4.3, 95% CI: 1.28–14.52) in multivariable analysis adjusting for potential confounders.
Conclusion: Infection with SARS-CoV-2 may be associated with increased odds of in-hospital mortality in ICH patients.

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be associated with potentially life-threatening thrombotic complications such as cerebrovascular and venous thromboembolic events. [1–4] The association of ischemic stroke with SARS-CoV-2 infection is implicated in multiple studies. [5–11] However, there are limited data in the literature describing hemorrhagic stroke in COVID-19 patients, mainly including case reports and case series. [12–14]

Intracerebral hemorrhage (ICH) is a devastating cerebrovascular event with a high mortality rate [15,16]. Glasgow Coma Scale (GCS) on admission, hemorrhage volume, presence of intraventricular hemorrhage (IVH), infratentorial site of hemorrhage, and higher age are associated with increased mortality [17]. The association of ICH development and its mortality with SARS-CoV-2 infection is not clear yet.

Herein, we presented a series of hospitalized ICH cases infected with SARS-CoV-2 and compared them with a cohort of non-SARS-CoV-2 infected ICH patients in terms of clinical outcome and in-hospital mortality. We also evaluated whether infection with SARS-CoV-2 could be a predictor of mortality in ICH patients.

2. Materials and methods

2.1. Study design and patients

This is a multicenter multinational observational study, conducted according to the guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [18] and Enhancing the QUAlity and Transparency Of health Research (EQUATOR) [19].

Adult hospitalized patients with the diagnosis of ICH and SARS-CoV-2 infection confirmed by reverse transcription-polymerase chain reaction (RT-PCR), were included. ICH was considered as any primary intraparenchymal hemorrhage (IPH) on the head computed tomography (CT) or brain magnetic resonance imaging (MRI) with or without intraventricular extension or subarachnoid hemorrhage. Other types of intracranial hemorrhage such as ischemic infarct with hemorrhagic transformation, subdural hemorrhage, epidural hemorrhage, subarachnoid hemorrhage alone, cerebral amyloid angiopathy and hemorrhagic leukoencephalopathy were excluded. We also excluded those patients with the diagnosis of SARS-CoV-2 infection onset earlier than three weeks prior to the ICH occurrence or beyond two days after ICH diagnosis.

The study was conducted by the investigators at the Neuroscience Institute of Geisinger Health System, Pennsylvania, USA, and was approved by the Institutional Review Board (IRB) of Geisinger Health System. The IRBs of other participating institutions approved the study protocol whenever required.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2. Data collection

The principal investigators of this study invited collaborators from several countries via phone calls or emails. We received the cases of ICH and SARS-CoV-2 infection from the beginning of the pandemic from 13 centers in the United States, Iran, Turkey, Spain, Greece, and Italy.

Data for each patient were gathered on a standardized electronic datasheet. Collaborators collected the data from patients' medical records, images on picture archiving and communication systems (PACS), and hospital information systems. The following variables were assessed: demographic data including age and sex, admission GCS and ICH Hemphill score and its components [17], timelines of SARS-CoV-2 infection and ICH, past medical history, medication history, admission lab data, radiological characteristics of ICH including location and volume of hemorrhage, discharge outcome based on modified Rankin Scale (mRS), length of hospital stay and in-hospital mortality.

For the control group, we used a dataset from a previous cohort of 107 ICH patients admitted between October 2015 and March 2016 [20], from Iran, the country where the majority of cases were recruited. Data harmonization was conducted to combine data from different sources and provide a comparable data view for analysis.

2.3. Outcome measure

The primary outcome measure in this study was in-hospital mortality, defined as the all-cause death during hospitalization.

2.4. Statistical analysis

We compared the baseline characteristics, laboratory and radiological findings, and outcomes between the ICH patients with SARS-CoV-2 infection and the control group, as well as within the group with ICH and SARS-CoV-2 infection, between dead and survived patients. We applied an independent sample *t*-test, Mann–Whitney *U* test, Chi-Square, and Fisher's exact tests for univariate analyses. Mean ± standard deviation (SD) or median (interquartile, IQR) was reported for quantitative variables, and frequencies and relative frequencies were reported for qualitative variables.

In addition, we assessed the association of SARS-CoV-2 infection and mortality in patients with ICH through logistic regression analysis. Assumptions for binary logistic regression analysis were met. We adjusted the model for age, admission GCS, presence of IVH, the volume of hemorrhage, and location of hemorrhage (infratentorial versus supratentorial). Crude and adjusted odds ratios (cOR and aOR) with 95% confidence interval (CI) were reported. A *P*-value of <0.05 was considered significant. SPSS software, version 23, was used for statistical analysis. [21]

3. Results

We received 70 cases presenting with ICH and positive for SARS-CoV-2 infection. Seven patients were excluded because they did not meet our timeline criteria. Among 63 included patients, the mean age was 61.4 ± 18.1, ranging from 18 to 94 years. Twenty-three patients (36.5%) were women.

Eleven cases (17.5%) in the COVID-19 group had no known ICH risk factors. In two patients, ICH presented before the COVID-19 diagnosis or symptom onset, and in the other 61 patients, ICH occurred on the same day or after COVID-19 onset or diagnosis. Table 1 compares baseline, and radiologic characteristics and in-hospital mortality between SARS-CoV-2 infected and SARS-CoV-2 non-infected ICH patients. Patients with SARS-CoV-2 infection were significantly younger ($P = 0.044$), had a higher ICH score ($P = 0.025$), a more frequent history of diabetes ($P = 0.007$), and significantly lower platelet count ($P < 0.001$). IVH occurred less frequently in SARS-CoV-2 infected cases ($P < 0.001$).

Duration of hospital stay was 12.4 ± 13.2 days in patients with

Table 1
Comparison of baseline and radiological characteristics and the outcome of ICH patients with SARS-CoV-2 infection with those without SARS-CoV-2 infection. ICH = Intracerebral Hemorrhage; INR = International Normalized Ratio; IQR = Interquartile Range; IVH = Intraventricular Hemorrhage; PTT = Partial Thromboplastin Time.

Variables	Current series (ICH patients with SARS-CoV2 infection) *N* = 63	Control group (ICH patients without SARS-CoV2 infection) *N* = 107	P-value
Demographic and baseline characteristics			
Age (years)	61.4 ± 18.1	66.8 ± 16.2	**0.044**
Female	23 (36.5%)	54 (50.5%)	0.077
Admission GCS (median (IQR))	11 (7–13)	9 (5–13)	0.215
ICH score (median (IQR))	3 (2–4)	2 (1–3)	**0.025**
Diabetes	21 (33.9%)	17 (15.9%)	**0.007**
Hypertension	47 (75.8%)	74 (69.2%)	0.356
History of trauma	0 (0.00%)	3 (2.8%)	0.299
Anti-coagulant use	4 (6.5%)	10 (9.3%)	0.511
Anti-Platelet use	26 (41.3%)		
Lab data			
INR	1.15 ± 0.64	1.24 ± 0.62	0.486
PTT	30.5 ± 8.2	32.8 ± 10.3	0.219
Platelet Count (Count x 10^9/L)	177.8 ± 77.8	240.5 ± 79.3	**<0.001**
Radiologic findings			
Supratentorial	52 (85.2%)	91 (85.0%)	0.972
Infratentorial	9 (14.8%)	16 (15.0%)	
Location of Hemorrhage:			
Basal Ganglia/ Thalamus	33 (55.9%)	52 (48.6%)	0.846
Lobar	9 (15.3%)	24 (22.4%)	
Cerebellar	3 (5.1%)	6 (5.6%)	
Brain stem	4 (6.8%)	8 (7.5%)	
Multiple	10 (16.9%)	17 (15.9%)	
Presence of IVH	14 (22.2%)	56 (52.3%)	**<0.001**
Volume of Hemorrhage (cm^3)	27.3 ± 32.0	26.1 ± 17.1	0.830
Outcome			
In-hospital mortality	41 (65.1%)	66 (61.7%)	0.658

SARS-CoV-2 infection, and ICH and 41 (65%) of these patients died during hospitalization. In the univariate analysis, in-hospital mortality did not differ cases and controls (65% vs. 62%; $P = 0.658$); however, in a multivariable model, after adjustment for age, admission GCS, presence of IVH, the volume of hemorrhage, and location of hemorrhage (infratentorial versus supratentorial), the presence of SARS-CoV-2 infection was significantly associated with higher rates of in-hospital mortality (aOR: 4.31, 95% CI: 1.28–14.52). (Table 2).

Table 3 shows the univariate comparison of the baseline and radiologic findings within the SARS-CoV-2 infected ICH cases between dead and survived patients. Lower admission GCS ($P = 0.001$), higher ICH score ($P = 0.001$), and higher volume of hemorrhage ($P < 0.001$) were independently associated with mortality.

4. Discussion

We presented a series of 63 ICH patients with concomitant SARS-CoV-2 infection. Compared to controls, ICH in SARS-CoV-2 infected patients occurred at a younger age and primarily in men (63.5%); this observation is consistent with the results of previous studies. [13,22,23] These patients had higher ICH scores, a more frequent history of diabetes, and lower platelet counts. The in-hospital mortality was 65% within the SARS-CoV-2 infected group. In multivariable analysis, SARS-CoV-2 infection was significantly associated with a four-fold increase in in-hospital mortality.

The majority of our cases had well-established risk factors which predisposed them to ICH, with hypertension being the most frequent one (75% of cases). This finding is in line with the result of the previous studies. [22,24] Eleven SARS-CoV-2 infected patients (17.5%) had no known ICH risk factors. It is not fully clear whether the SARS-CoV-2 infection could contribute to ICH development or these two conditions occurred coincidentally. Hospitalized patients with COVID-19 receive prophylactic or therapeutic doses of anticoagulants according to the current guidelines. [25] Anticoagulation is considered associated with ICH occurrence in several studies. [26,27] However, in this series, only

Table 2
Logistic regression analysis of predictors of mortality in patients with ICH. GCS = Glasgow Coma Scale; ICH = Intracerebral Hemorrhage; IVH = Intraventricular Hemorrhage; OR = Odds Ratio.

Variable	Crude OR	Adjusted OR	95% CI	P-value
SARS-CoV-2 infection	1.16	4.31	1.28–14.52	**0.018**
Age	1.02	1.07	1.03–1.11	**<0.001**
Admission GCS	0.691	0.716	0.611–0.838	**<0.001**
Presence of IVH	2.36	3.09	1.10–8.67	**0.032**
Bleeding Volume	1.06	1.06	1.02–1.09	**0.003**
Infratentorial location of ICH	1.08	2.35	0.467–11.87	0.300

Table 3
Comparison of baseline and radiological characteristics of ICH patients with SARS-CoV-2 infection between dead and survived patients. GCS = Glasgow Coma Scale; ICH = Intracerebral Hemorrhage; INR = International Normalized Ratio; IQR = Interquartile Range; IVH = Intraventricular Hemorrhage; PTT = Partial Thromboplastin Time.

Variables	Deceased *N* = 41	Survived *N* = 22	*P*-value
Demographic and baseline characteristics			
Age (years)	62.7 ± 19.2	58.9 ± 15.9	0.423
Female	17 (41.5%)	6 (27.3%)	0.265
Admission GCS (median (IQR))	8.5 (6.25–12)	13 (11.5–15)	**0.001**
ICH score (median (IQR))	3 (2–4)	2 (1–3)	**0.001**
History of diabetes	15 (37.5%)	6 (27.3%)	0.416
History of hypertension	33 (82.5)	14 (63.6%)	0.097
History of trauma	0 (0.0%)	0 (0.0%)	
Anti-coagulant use	3 (7.5%)	1 (4.5%)	1.000
Anti-Platelet use	17 (42.5%)	9 (40.9%)	0.903
Lab data			
INR	1.16 ± 0.79	1.14 ± 0.15	0.952
PTT (s)	30.1 ± 9.5	31.3 ± 5.2	0.687
Platelet Count (Count x 10^9/L)	184.9 ± 76.4	164.7 ± 80.8	0.355
Radiologic findings			
Supra-tentorial	34 (87.2%)	18 (81.8%)	0.710
Infra-tentorial	5 (12.8%)	4 (18.2%)	
Location of Hemorrhage:			
Basal Ganglia/Thalamus	23 (59.0%)	10 (50.0%)	0.232
Lobar	4 (10.3%)	5 (25.0%)	
Cerebellum	1 (2.6%)	2 (10.0%)	
Brain stem	4 (10.3%)	0 (0.0%)	
Multiple	7 (17.9%)	3 (15.0%)	
Presence of IVH	9 (22.0%)	5 (22.7%)	1.000
Volume of Hemorrhage (cm^3)	37.9 ± 34.7	7.2 ± 8.4	**<0.001**

three patients were on anticoagulant therapy prior to the ICH development since the majority of patients were recruited at the beginning of the pandemic when routine administration of anticoagulation in COVID-19 patients was uncommon. It has been suggested that besides the well-established risk factors and anticoagulant administration, additional mechanisms might lead to ICH occurrence in SARS-CoV-2 infected patients. SARS-CoV-2 neurotropism, direct endothelial cell invasion via SARS-CoV-2 entry protein, angiotensin-converting enzyme 2 (ACE2) and resulting endothelitis, pro-inflammatory cytokines-associated vascular wall remodeling and disintegrity, hypertension induced by downregulation of ACE2 and unopposed effects of renin-angiotensin II-aldosterone system (RASS) are among the potential mechanisms through which SARS-CoV2 predispose patients to the ICH. [28–33] Another notable mechanism that can predispose patients with COVID-19 to hemorrhage is dysfunction in the coagulation cascade and fibrinolytic homeostasis. Zuo et.al reported that tissue plasminogen activator (tPA) is markedly elevated in hospitalized COVID-19 patients and is associated with mortality. [34]

A pooled analysis of previous studies showed that ICH could occur in COVID-19 patients with an incidence ranging from 0.13 to 2.03% and mortality of 54%. [13] The rate of mortality in our study was higher, probably because the majority of our cases were recruited from Iran, a developing country with limited resources. The in-hospital mortality rate in cases was similar to a previous cohort of non-COVID-19 ICH patients from Iran [17], which we used as the control group (65% in SARS-CoV-2 infected patients versus 62% in non-SARS-CoV-2 infected control group). Our results showed that after adjustment for other known predictors of ICH mortality [17], SARS-CoV-2 infection was associated with an increased risk of in-hospital mortality in ICH patients. Pulmonary involvement and respiratory compromise, systemic inflammation, and multi-organ failure in severe COVID-19 might worsen the ICH outcome, as such could occur while COVID-19 accompanies other comorbidities other than ICH. [35] According to the univariate analysis, among SARS-CoV-2 infected patients, lower GCS and the higher ICH score on admission, and the larger hematoma volume were significantly associated with in-hospital mortality. Previous studies on the predictors of ICH mortality demonstrated similar findings. [17,36,37]

The current study has several methodological shortcomings. One limitation is that the data on COVID-19 severity was not available for most cases. Therefore, we were not able to assess the association of COVID-19 severity with in-hospital mortality. Also, the study's retrospective nature led to missing data in some variables, such as laboratory findings. In addition, the small sample size of SARS-CoV-2 patients with ICH decreased the power of the study. Nevertheless, this is the largest case series on SARS-CoV-2 patients developing ICH to the best of our knowledge. Furthermore, we selected and used the data of a historical cohort collected in 2015–2016 as the control group. The variation in demographics between the two cohorts might limit the strength of our comparison. Also, since the care of ICH patients has improved in recent years, the time variation between these two studies might be a source of bias.

5. Conclusions

ICH “in association” with SARS-CoV-2 infection, may increase the mortality risk compared to non-SARS-CoV-2 infected patients. Therefore, we suggest close monitoring of neurological manifestations and deterioration in COVID-19 patients, especially those with underlying ICH risk factors.

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Declaration of Competing Interest

None.

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