Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Subarachnoid Hemorrhage and COVID-19: An Analysis of 282,718 Patients

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BACKGROUND: **Intracranial hemorrhage (including subarachnoid hemorrhage [SAH]) has been reported in 0.3%–1.2% of patients with coronavirus disease 2019 (COVID-19). However, no study has evaluated the risk of SAH in patients with COVID-19.**

METHODS: **We analyzed data from 62 health care facilities using the Cerner de-identified COVID-19 dataset.**

RESULTS: **There were 86 (0.1%) and 376 (0.2%) patients with SAH among 85,645 patients with COVID-19 and 197,073 patients without COVID-19, respectively. In the multivariate model, there was a lower risk of SAH in patients with COVID-19 (odds ratio 0.5, 95% confidence interval 0.4–0.7, $P < 0.0001$) after adjusting for sex, age strata, race/ethnicity, hypertension, and nicotine dependence/tobacco use. The proportions of patients who developed pneumonia (58.1% vs. 21.3%, $P < 0.0001$), acute kidney injury (43% vs. 27.7%, $P = 0.0005$), septic shock (44.2% vs. 20.7%, $P < 0.0001$), and respiratory failure (64.0% vs. 39.1%, $P < 0.0001$) were significantly higher among patients with SAH and COVID-19 compared with patients without COVID-19. The in-hospital mortality among patients with SAH and COVID-19 was significantly higher compared with patients without COVID-19 (31.4% vs. 12.2%, $P < 0.0001$).**

CONCLUSIONS: **The risk of SAH was not increased in patients with COVID-19. The higher mortality in patients with SAH and COVID-19 compared with patients without COVID-19 is likely mediated by higher frequency of systemic comorbidities.**

INTRODUCTION

Intracranial hemorrhage (including subarachnoid hemorrhage [SAH]) has been reported in 0.3%–1.2% of patients with coronavirus disease 2019 (COVID-19) based on a review of 9 cohort studies (N = 13,741 patients).[1] Isolated aneurysmal and nonaneurysmal SAHs in patients with COVID-19 have been reported previously.[2-4] Although previous studies have evaluated the risk of ischemic stroke,[5,6] no study has evaluated the risk of SAH in patients with COVID-19. We performed this study to identify risk factors, comorbidities, treatment strategies, and outcomes in patients with SAH derived from a large cohort of COVID-19 patients.

MATERIAL AND METHODS

We analyzed the data from the Cerner de-identified COVID-19 dataset, a subset of Cerner Real-World Data extracted from the electronic medical records of health care facilities that have a data use agreement with Cerner Corporation (North Kansas City, Missouri, USA).[7-9] The COVID-19 de-identified dataset includes data for patients who qualified for inclusion based on the following criteria: 1) patient had a minimum of 1 emergency department or inpatient encounter with a diagnosis code that could be associated with COVID-19 exposure or infection; 2)

Key words
- COVID-19
- Death
- Disability
- Electronic medical records
- SARS-CoV-2
- Subarachnoid hemorrhage

Abbreviations and Acronyms
CI: Confidence interval
COVID-19: Coronavirus disease 2019
ICD-10-CM: *International Classification of Diseases, Tenth Revision, Clinical Modification*
OR: Odds ratio
SAH: Subarachnoid hemorrhage

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patient had a minimum of 1 emergency department or inpatient encounter with a positive laboratory test for COVID-19.

The methodological aspects of the dataset are available in another publication.[9,10] The Cerner Real World Data-COVID-2020Q3 version is based on electronic medical encounters between December 1, 2019, and November 13, 2020, from 62 contributing Cerner Real-World Data health systems. Our analysis included only hospitalized patients with prior medical history to ensure completeness of the records of potential comorbidities. Patients with some prior medical history constituted approximately 67% of the total cohort.

We used the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) primary diagnosis code I60 to identify patients admitted with SAH. *ICD-10-CM* codes were also used to identify patients with hypertension (I10, O10.0, O10.9, I16, I67.4), diabetes mellitus (E08), nicotine dependence (F17), hyperlipidemia (E78), atrial fibrillation (I48), and congestive heart failure (I09.81, I11.0, I50). *ICD-10-CM* secondary diagnosis codes were used to identify patients with SAH-associated complications, such as ischemic stroke (including cerebral ischemia) (I63, I65, I66, I67.81, I67.82, I67.89), cerebral edema (G93.5, G93.6), vasospasm (I67.84), acute kidney injury (N17), hepatic failure (K72), cardiac arrest (I46), systemic inflammatory response syndrome (R65.1), respiratory failure (J96), pneumonia (J12–J18), urinary tract infection (N30.0, N30.9, N34.1, N34.2, N39.0), septic shock (A41 and R65.21), deep venous thrombosis (I82), pulmonary embolism (I26), intracerebral hemorrhage (I61, I62.9), and acute myocardial infarction (I21). We also used *ICD-10-CM* procedure codes and *Current Procedural Terminology* codes to estimate the proportion of patients with SAH who underwent aneurysm treatment using surgical or endovascular treatment identified by *ICD-10-PCS* (procedure coding system) (03VG0CZ for surgical, 03LG3DZ for endovascular) or angioplasty (procedure codes 037G3DZ, 037G3ZZ). Intubation and mechanical ventilation were identified by *ICD-10-CM* codes 0BH17EZ and Z9911 or *Current Procedural Terminology* codes 31500, 94656, and 94657 (for intubation) or 94002–94005 (for mechanical ventilation).

The outcome was based on discharge destination and categorized as home or nonroutine discharge. Discharge destination to home has been shown to predict no to mild disability, whereas nonroutine discharge predicts moderate to severe disability at 3 months after stroke.[11,12]

Statistical Analysis

We performed this analysis to identify any significant differences in clinical characteristics between patients with SAH with and without COVID-19 as well as patients with COVID-19 with and without SAH. We performed logistic regression analysis including all patients in the dataset to identify the association between COVID-19 and SAH. We adjusted for known risk factors for SAH, including age (age strata <35, 35–54, 55–70, and >70 years), sex, race/ethnicity, hypertension, nicotine dependence, and previous SAH. All analyses were done using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

There were 85,645 patients with confirmed COVID-19 among 282,718 patients in the Cerner de-identified COVID-19 dataset. Among 85,645 patients with COVID-19, 86 (0.1%) patients developed SAH. Among 197,073 patients in whom COVID-19 was excluded, 376 (0.2%) patients developed SAH.

Comparison Between SAH Patients with and without COVID-19

Aneurysm treatment using an endovascular procedure was performed in none of the 85 patients with COVID-19 and SAH and in 12 of the 376 patients without COVID-19 with SAH. Aneurysm treatment using a surgical procedure was performed in 2 of the 376 patients without COVID-19 with SAH. The in-hospital mortality among patients with SAH and COVID-19 was significantly higher compared with patients without COVID-19 (31.4% vs. 12.2%, $P < 0.0001$) (Table 1).

Results of Multivariate Analysis

In the multivariate model, there was a lower risk of SAH in patients with COVID-19 (odds ratio [OR] 0.5, 95% confidence interval [CI] 0.4–0.7, $P < 0.0001$) after adjusting for sex, age strata, race/ethnicity, hypertension, and nicotine dependence/tobacco use. Other risk factors independently associated with SAH were age 35–54 years (OR 1.8, 95% CI 1.2–2.5, $P = 0.002$), age 55–70 years (OR 2.6, 95% CI 1.8–3.7, $P < 0.0001$), age >70 years (OR 3.0, 95% CI 2.1–4.3, $P < 0.0001$), and hypertension (OR 1.7, 95% CI 1.3–2.1, $P < 0.0001$).

Comparison Between COVID-19 Patients with and without SAH

During the COVID-19 admissions, pneumonia, pulmonary embolism, urinary tract infection, acute kidney injury, hepatic failure, cardiac arrest, acute myocardial infarction, septic shock, and respiratory failure were more frequent in patients with COVID-19 and SAH. The in-hospital mortality among patients with COVID-19 and SAH was significantly higher compared with patients with COVID-19 without SAH (31.4% vs. 6.8%, $P < 0.0001$) (Table 1).

DISCUSSION

COVID-19 and Risk of SAH

We found a low occurrence (0.1%) of SAH among patients with COVID-19. A slightly higher prevalence (0.2%) of SAH was seen among patients without COVID-19 in our analysis. It appeared that most SAHs were nonaneurysmal in nature.[13] Aneurysm treatment using an endovascular or a surgical procedure was performed in none of the 86 patients with COVID-19 and SAH and in 14 of the 376 patients without COVID-19 with SAH. In contrast, approximately 40% of patients admitted with SAH in the Nationwide Inpatient Sample received either endovascular or surgical treatment,[14] highlighting differences in characteristics of SAHs between study populations. A previous study in France from 6 neurosurgical departments reported that the number of admissions for aneurysmal SAH decreased during the COVID-19 pandemic.[15] Another report from 18 institutions reported that the number of endovascular treatments for ruptured intracranial aneurysms decreased between January–February (early phase) and March–April (established phase) of the COVID-19 pandemic (7.3% reduction).[16]

Our results contradict the assumption of higher risk of SAH in COVID-19 based on individual case reports.[2-4] Previous studies

Table 1. Demographic and Clinical Characteristics and Outcome of Patients According to COVID-19 Status and Occurrence of Subarachnoid Hemorrhage

	Patients with SAH and COVID-19 (n = 86)	Patients with SAH but without COVID-19 (n = 376)	Patients with COVID-19 but without SAH (n = 85,559)
Age, years			
Mean ± SD*	60.5 ± 17.7	62.0 ± 19.6	49.7 ± 21.3
<35*	10 (11.6%)	43 (11.4%)	24,940 (29.1%)
35–54	16 (18.6%)	73 (19.4%)	23,189 (27.1%)
55–70*†	35 (40.7%)	111 (29.5%)	20,417 (23.9%)
>70*	25 (29.1%)	149 (39.6%)	17,013 (19.9%)
Sex			
Men	47 (54.7%)	167 (44.4%)	38,650 (45.2%)
Women	39 (45.3%)	206 (54.8%)	46,533 (54.4%)
Race/ethnicity			
White, non-Hispanic†	28 (32.6%)	203 (54%)	26,596 (31.1%)
African American†	17 (19.8%)	44 (11.7%)	16,346 (19.1%)
Hispanic	30 (34.9%)	94 (25%)	33,774 (39.5%)
Other	11 (12.8%)	35 (9.3%)	8843 (10.3%)
Hypertension*	59 (68.6%)	277 (73.7%)	40,822 (47.7%)
Diabetes mellitus	29 (33.7%)	130 (34.6%)	26,352 (30.8%)
Nicotine dependence/tobacco use*	24 (27.9%)	99 (26.3%)	13,489 (15.8%)
Hyperlipidemia*	42 (48.8%)	187 (49.7%)	29,138 (34.1%)
Atrial fibrillation*	25 (29.1%)	87 (23.1%)	8615 (10.1%)
Congestive heart failure*	18 (20.9%)	96 (25.5%)	10,705 (12.5%)
Previous SAH*	12 (14%)	52 (13.8%)	172 (0.2%)
In-hospital events			
Length of hospitalization, days, mean ± SD*†	22 ± 21	10 ± 12	10 ± 12
Ischemic stroke, including cerebral ischemia*	21 (24.4%)	88 (23.4%)	1693 (2%)
Cerebral vasospasm*	2 (2.3%)	12 (3.2%)	3 (0%)
Intracerebral hemorrhage*	25 (29.1%)	122 (32.4%)	191 (0.2%)
New transient cerebral ischemic attacks	1 (1.2%)	3 (0.8%)	255 (0.3%)
Cerebral edema*	21 (24.4%)	94 (25%)	211 (0.2%)
Pneumonia*†	50 (58.1%)	80 (21.3%)	32,602 (38.1%)
Deep venous thrombosis	4 (4.7%)	29 (7.7%)	1646 (1.9%)
Pulmonary embolism*	6 (7%)	13 (3.5%)	1349 (1.6%)
Urinary tract infection*	16 (18.6%)	72 (19.1%)	7361 (8.6%)
Acute kidney injury*†	37 (43%)	104 (27.7%)	12,759 (14.9%)
Hepatic failure*	5 (5.8%)	18 (4.8%)	948 (1.1%)
Cardiac arrest*	6 (7%)	23 (6.1%)	1520 (1.8%)
Acute myocardial infarction*	6 (7%)	30 (8%)	2208 (2.6%)
SIRS	0 (0%)	5 (1.3%)	732 (0.9%)

SAH, subarachnoid hemorrhage; COVID-19, coronavirus disease 2019; SIRS, systemic inflammatory response syndrome.
*Significant difference between COVID-19 patients with SAH compared with COVID-19 patients without SAH.
†Significant difference between SAH patients with COVID-19 compared with SAH patients without COVID-19.

Continues

Table 1. Continued

	Patients with SAH and COVID-19 (n = 86)	Patients with SAH but without COVID-19 (n = 376)	Patients with COVID-19 but without SAH (n = 85,559)
Septic shock*†	38 (44.2%)	78 (20.7%)	12,156 (14.2%)
Respiratory failure*†	55 (64%)	147 (39.1%)	21,922 (25.6%)
Received intubation/mechanical ventilation*	20 (23.3%)	65 (17.3%)	3716 (4.3%)
Received angioplasty*	1 (1.2%)	1 (0.3%)	1 (0%)
Received ventriculostomy*	2 (2.3%)	28 (7.4%)	15 (0%)
Received coil placement	0 (0%)	12 (3.2%)	4 (0%)
Received clip placement	0 (0%)	2 (0.5%)	1 (0%)
Received intraventricular catheter*	2 (2.3%)	26 (6.9%)	11 (0%)
Received intracranial pressure monitor	0 (0%)	5 (1.3%)	2 (0%)
Received tracheostomy*	7 (8.1%)	15 (4%)	419 (0.5%)
Outcome			
Nonroutine discharge or in-hospital death*	60 (69.8%)	247 (65.7%)	22,117 (25.8%)
Died in hospital*†	27 (31.4%)	46 (12.2%)	5834 (6.8%)

SAH, subarachnoid hemorrhage; COVID-19, coronavirus disease 2019; SIRS, systemic inflammatory response syndrome.
*Significant difference between COVID-19 patients with SAH compared with COVID-19 patients without SAH.
†Significant difference between SAH patients with COVID-19 compared with SAH patients without COVID-19.

showed that severe acute respiratory syndrome coronavirus 2 infection causes a profound proinflammatory thrombotic state rather than hemorrhagic events[6,17,18] with excessive cytokine release activation of monocytes and neutrophils and endothelium activation and dysfunction. Elevated concentration of proinflammatory cytokines, especially tumor necrosis factor-α, interleukin-6, and interleukin-10 (cytokine storm), has been reported in patients with COVID-19.[19,20] Higher thrombogenicity among patients with COVID-19 is also evident by the frequent occurrence of coronary and cerebral arterial ischemic events[5,21] and venous thrombosis involving the peripheral and pulmonary circulation.[22,23]

A potential mechanism for nonaneurysmal SAH may be vasculitis involving the medium- and small-sized arteries in the brain diagnosed by neuroimaging in patients with COVID-19.[24-26] Endothelial cell inclusion bodies, apoptosis, and diffuse endothelial inflammation has been reported in patients with COVID-19 in various vascular beds.[27] Keller et al.[26] reported 2 patients with COVID-19 in whom SAH was diagnosed. One patient presented with SAH adjacent to the right frontal lobe, and vessel wall enhancement was seen in the left middle cerebral artery and right posterior cerebral artery on high-resolution magnetic resonance imaging of the vessel wall. Another patient died of acute respiratory distress and massive liver cell necrosis and underwent an autopsy. Endotheliitis affecting small intestinal, myocardial, and renal vessels was seen. Brain specimens demonstrated microbleeds in the pontine tegmentum and microinfarcts in the basal ganglia. Extensive SAH was seen around the rostral surface of the cerebellum. Adjacent cerebral tissue showed multiple fresh microinfarcts and parenchymal hemorrhages.

Effect of COVID-19 on Outcomes for SAH Patients

The in-hospital mortality among patients with SAH and COVID-19 was significantly higher compared with patients without COVID-19. A higher rate of cerebral ischemia in patients with COVID-19 and SAH was expected based on severe acute respiratory syndrome coronavirus 2 causing a profoundly proinflammatory thrombotic state as discussed above.[6,17,18] Patients with SAH and COVID-19 had higher rates of pneumonia, pulmonary embolism, and acute kidney injury, which may explain the higher mortality observed. Previous studies have shown that pneumonias and infections increase the risk of death or disability in patients with SAH.[28-30]

The multiple organ dysfunction seen in patients with SAH and COVID-19[31,32] was far more pronounced than in patients with COVID-19 without SAH. Patients with COVID-19 who had SAH had higher mortality than patients without SAH. Previous studies have demonstrated an inflammatory response, such as elevated concentration of interleukin-6, in patients with SAH[33,34] as a consequence of initial hemorrhage, which may exacerbate the inflammatory response to COVID-19. Furthermore, patients with SAH have high rates of multiple organ dysfunction regardless of COVID-19 infection,[35-37] supporting a direct contribution of SAH.

Implications for Practice

The high rate of discharge to destination other than home or death in patients with SAH with COVID-19 may be related to multiple organ dysfunction/failure and is unlikely to be influenced from treatment of neurological aspects of SAH alone. An assessment of the magnitude of multiple organ dysfunction may be helpful in delineating the overall care paradigm in patients with SAH. Several factors in patients with COVID-19 have been

established that can identify the patients at risk for in-hospital mortality, such as older age, high Sequential Organ Failure Assessment score, cardiovascular diseases, secondary infections, acute respiratory distress syndrome, acute renal injury, and laboratory findings of lymphopenia and elevated hepatic enzymes, C-reactive protein, ferritin, creatinine phosphokinase, and fibrin D-dimers.[38-41] Therefore, assessment of dysfunction in other organs using validated systems such as Sequential Organ Failure Assessment appears to be important to provide overall prognosis before determining the appropriate SAH treatment.

Limitations

Our analyses used the Cerner de-identified COVID-19 dataset derived from a large number of health care facilities. However, the dataset provides minimal details on the severity of neurological deficits and diagnostic study results, and therefore the exact reasons for differences in outcomes between patients with SAH and COVID-19 and patients with SAH without COVID-19 could not be determined at a granular level. The dataset also depends on the accuracy of diagnosis and procedures listed in the data collection system. *ICD-10-CM* diagnosis codes have a high positive predictive value (96%) to identify SAH from the principal discharge diagnosis.[42]

The discharge functional outcome cannot be measured with the available data, and the closest index was using the destination of discharge as done in previous studies using the Nationwide Inpatient Sample data.[11,43] Discharge to home has a very high negative predictive value (ability to exclude) for patients with a modified Rankin Scale score of 2–6 at 3 months.[12] Therefore, discharge destination may allow differentiation of patients with different functional outcomes with a reasonable level of accuracy. The patients with SAH without COVID-19 in the dataset were patients who were screened for COVID-19 owing to either history of exposure or respiratory symptoms. These patients may have a clinical presentation suggestive of respiratory tract infections, which could mean that they may have other respiratory tract infections, or even a small minority could have undetected COVID-19 depending on the screening tests undertaken.[44-46] As our analysis included only patients who were hospitalized, patients with SAH with mild symptoms may not have been admitted and thus may be underrepresented. This underrepresentation is particularly prominent during the COVID-19 pandemic because patients with mild diseases are avoiding hospitalization in an effort to reduce exposure to COVID-19.[47]

CONCLUSIONS

SAH was infrequent and the risk was not increased in patients with COVID-19. The risk of death was increased in patients with SAH and COVID-19 compared with patients with SAH without COVID-19 and patients with COVID-19 without SAH. Part of the increased risk was likely mediated through higher frequency of systemic comorbidities in these patients.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Adnan I. Qureshi: Conceptualization, Methodology, Investigation, Writing - original draft, Supervision, Project administration, Funding acquisition. **William I. Baskett:** Methodology, Software, Formal analysis, Resources, Data curation, Writing - review & editing. **Wei Huang:** Formal analysis, Writing - review & editing. **Daniel Shyu:** Methodology, Writing - review & editing. **Danny Myers:** Investigation, Resources, Data curation, Writing - review & editing. **Iryna Lobanova:** Conceptualization, Writing - review & editing. **Muhammad F. Ishfaq:** Conceptualization, Writing - review & editing. **S. Hasan Naqvi:** Conceptualization, Writing - review & editing. **Brandi R. French:** Conceptualization, Writing - review & editing. **Farhan Siddiq:** Conceptualization, Writing - review & editing. **Camilo R. Gomez:** Conceptualization, Writing - review & editing. **Chi-Ren Shyu:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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