University of Texas Rio Grande Valley

ScholarWorks @ UTRGV

School of Medicine Publications and Presentations

School of Medicine

1-31-2024

COVID-19 Infection Is Associated With Poor Outcomes in Patients With Intracerebral Hemorrhage

Daniela Renedo

Audrey C. Leasure

Rebecca Young

Cyprien A. Rivier

Brooke Alhanti

See next page for additional authors

Follow this and additional works at: https://scholarworks.utrgv.edu/som_pub

 Part of the Medicine and Health Sciences Commons

Authors

Daniela Renedo, Audrey C. Leasure, Rebecca Young, Cyprien A. Rivier, Brooke Alhanti, Brian Mac Grory, Steven R. Messe, Mathew J. Reeves, Ameer E. Hassan, and Lee Schwamm

Check for updates

Journal of the American Heart Association

ORIGINAL RESEARCH

COVID-19 Infection Is Associated With Poor Outcomes in Patients With Intracerebral Hemorrhage

Daniela Renedo, MD*; Audrey C. Leasure, MD*; Rebecca Young, MS; Cyprien A. Rivier, MD, MSc; Brooke Alhanti, PhD; Brian Mac Grory, MB, BCh, BAO, MHSc, MRCP; Steven R. Messe, MD; Mathew J. Reeves, MD; Ameer E. Hassan DO; Lee Schwamm, MD; Adam de Havenon, MD, MSc; Charles C. Matouk, MD; Kevin N. Sheth, MD†; Guido J. Falcone, MD, ScD, MPH†

BACKGROUND: Patients with ischemic stroke and concomitant COVID-19 infection have worse outcomes than those without this infection, but the impact of COVID-19 on hemorrhagic stroke remains unclear. We aimed to assess if COVID-19 worsens outcomes in intracerebral hemorrhage (ICH).

METHODS AND RESULTS: We conducted an observational study of ICH outcomes using Get With The Guidelines Stroke data. We compared patients with ICH who were COVID-19 positive and negative during the pandemic (March 2020–February 2021) and prepandemic (March 2019–February 2020). Main outcomes were poor functional outcome (defined as a modified Rankin scale score of 4 to 6 at discharge), mortality, and discharge to a skilled nursing facility or hospice. The first stage included 60 091 patients with ICH who were COVID-19 negative and 1326 COVID-19 positive. In multivariable analyses, patients with ICH with versus without COVID-19 infection had 68% higher odds of poor outcome (odds ratio [OR], 1.68 [95% CI, 1.41–2.01]), 51% higher odds of mortality (OR, 1.51 [95% CI, 1.33–1.71]), and 66% higher odds of being discharged to a skilled nursing facility/hospice (OR, 1.66 [95% CI, 1.43–1.93]). The second stage included 62 743 prepandemic and 64 681 intrapandemic cases with ICH. In multivariable analyses, patients with ICH admitted during versus before the COVID-19 pandemic had 10% higher odds of poor outcomes (OR, 1.10 [95% CI, 1.07–1.14]), 5% higher mortality (OR, 1.05 [95% CI, 1.02–1.08]), and no significant difference in the risk of being discharged to a skilled nursing facility/hospice (OR, 0.93 [95% CI, 0.90–0.95]).

CONCLUSIONS: The pathophysiology of the COVID-19 infection and changes in health care delivery during the pandemic played a role in worsening outcomes in the patient population with ICH.

Key Words: COVID-19 ■ Get With The Guidelines Stroke ■ intracerebral hemorrhage ■ modified Rankin scale

COVID-19 can significantly worsen vascular diseases through activation of the coagulation cascade, activation of platelet-related pathways, and exacerbation of inflammatory responses.[1–3] Several studies have shown that COVID-19 leads to a higher risk of, and worse outcomes after, ischemic stroke.[4–7] However, the role of COVID-19 in hemorrhagic stroke remains understudied, largely due to the difficulty of attaining the necessary sample size to meaningfully study this question in a relatively rare stroke subtype. A

Correspondence to: Guido J. Falcone, MD, ScD, MPH, Department of Neurology, Yale School of Medicine, 100 York Street, Office 111, New Haven, CT 06511. Email: guido.falcone@yale.edu

*D. Renedo and A. C. Leasure are co-first authors.

†K. N. Sheth and G. J. Falcone jointly supervised this work.

Preprint posted on MedRxiv May 05, 2023. doi: https://doi.org/10.1101/2023.05.03.23289488.

This article was sent to Neel S. Singhal, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.030999

For Sources of Funding and Disclosures, see page 9.

© 2024 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

Downloaded from http://ahajournals.org by on February 1, 2024

CLINICAL PERSPECTIVE

What Is New?

- This observational study, based on a large data set from the multicenter Get With The Guidelines Stroke registry, demonstrates that patients with spontaneous intracerebral hemorrhage who also have COVID-19 infection experience significantly worse outcomes than those without this infection.

What Are the Clinical Implications?

- These findings suggest that the pathophysiology of COVID-19 infection and changes in health care delivery during the pandemic have adversely affected outcomes in this patient population. This highlights the importance of mitigating the effects of COVID-19 infection in patients with intracerebral hemorrhage and adjusting health care delivery protocols during pandemic situations.

Nonstandard Abbreviations and Acronyms

GWTG-Stroke	Get With The Guidelines Stroke
ICH	intracerebral hemorrhage

previous study showed that patients with spontaneous intracerebral hemorrhage (ICH) or nontraumatic subarachnoid hemorrhage and comorbid COVID infection were more likely to have diabetes, to be obese, and to have higher rates of death when compared with controls.[8]

To address these limitations, we employed the American Heart Association GWTG (Get With The Guidelines)-Stroke, an ongoing national registry of patients hospitalized for stroke.[9] With data contributions from more than 2000 hospitals across the country, GWTG significantly facilitates new discoveries in areas of stroke research where the stroke type, exposure, or outcome are rare or infrequent.[9,10]

In this context, we conducted an observational study with 2 main objectives. Our primary research question was to explore the differences in outcomes between patients with ICH who were COVID-19 positive and negative. Second, we aimed to investigate whether there were differences in outcomes in patients with ICH before and during the pandemic. By leveraging the unique platform of the GWTG-Stroke registry, this study seeks to shed light on the clinical evolution of patients with primary, nontraumatic ICH during the COVID-19 pandemic.

METHODS

The data that support the findings of this study are available from the GWTG-Stroke registry. These data are housed in the Precision Medicine Platform (https://precision.heart.org/about) and can be accessed upon request and approval by their commission. The methods used in this study are included within the article.

Study Design

We performed a retrospective, observational, cohort study using data from patients with ICH enrolled in GWTG-Stroke, an ongoing registry that currently includes more than 2000 hospitals and more than 4 million patients.[9–12] Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by their institutional review board. In addition, the institution-wide institutional review board for the American Heart Association determined that this study is exempt from oversight. Deidentified patient data from participant hospitals is entered into the GWTG-Stroke database. Variables collected include demographic characteristics, medical history, clinical outcomes, mortality, and discharge destination. Using these data, we carried out a 2-stage analysis using the data collected. In the first stage, we focused on patients with ICH who were admitted during the pandemic period from March 2020 to February 2021. We compared the functional outcomes and mortality rates between those patients who were infected with COVID-19 and those who were not.

In the second stage of our analysis, we aimed to provide a comprehensive overview of the pandemic's impact on ICH outcomes by comparing prepandemic and pandemic periods. Importantly, this comparison included all patients with ICH admitted during these periods, regardless of their COVID-19 status. Although this approach does not isolate the direct effect of COVID-19 infection on outcomes, it allows us to capture the full scope of the pandemic's impact, including potential indirect effects such as changes in health care delivery. We believe this comprehensive approach provides a more realistic picture of the challenges faced by patients with ICH during the pandemic.

This 2-stage design allowed us to examine both the specific impact of COVID-19 on patients with ICH and the general impact of the pandemic on ICH outcomes.

Ascertainment of ICH Cases

In GWTG–Stroke, trained hospital personnel ascertained ICH cases of patients 18 years of age or older using a combination of clinical data available in the

Downloaded from http://ahajournals.org by on February 1, 2024

patient's medical chart, review of neuroimaging and review of discharge *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (*ICD-9* and *ICD-10*) codes. For clarity, the ICH variable used in our study encompasses all types of (ICHs). However, we specifically excluded aneurysmal subarachnoid hemorrhage and spontaneous subdural hemorrhage from our analysis. Data are entered in the Patient Management Tool, a web-based tool designed to facilitate and standardize the collection of relevant data for each case.[9]

Ascertainment of COVID-19

Patients were considered COVID-19 positive if they were positive at the time of admission or at any point during the hospitalization. A dedicated variable for COVID-19 status was added to the GWTG–Stroke platform on April 1, 2020.[13]

Outcomes

Our primary outcome of interest was post-ICH functional status, evaluated through the modified Rankin scale at discharge, a 6-category (including 0) scale where 0=complete recovery with no residual symptoms; 1=no significant disability, able to carry out all usual activities despite some symptoms; 2=slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; 3=moderate disability, requires some help but able to walk unassisted; 4=moderately severe disability, unable to attend to own bodily needs without assistance and unable to walk unassisted; 5=severe disability, requires constant nursing care and attention and is bedridden/incontinent; and 6=death. Secondary outcomes included in-hospital death, discharge disposition (dichotomized as skilled nursing facility [SNF] or hospice versus home, inpatient rehabilitation facility, intermediate care, or long-term care) and length of stay.

Covariates

Other variables used in this study included demographic characteristics (age, sex, and race or ethnicity), medical history (prior coronary artery disease, atrial fibrillation, heart failure, stroke, and chronic kidney failure), vascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking, sleep apnea, and alcohol/drug abuse), pre-ICH medications (antiplatelets and anticoagulants), pre-ICH functional status; baseline physiological variables (blood pressure, heart rate, and respiratory rate), and information related to the admission (arrival via emergency medical services, arrival on or off hours, admission National Institutes of Health Stroke Scale score, baseline laboratory values).

Statistical Analysis

We used counts (percentages [%]) to describe discrete variables and mean (SD) to describe continuous variables. For unadjusted associations, we used chi-square or Wilcoxon rank-sum tests, as appropriate. We used multivariable logistic regression models when evaluating post-ICH functional status, in-hospital mortality, and discharge disposition. Multivariable models were adjusted for universal confounders (patient age, sex, and race or ethnicity), vascular risk factors (hypertension, hyperlipidemia, diabetes, smoking, and obesity), comorbidities (prior coronary artery disease, atrial fibrillation, heart failure, stroke, and chronic kidney failure), relevant medications (antiplatelets and anticoagulants), and pre-ICH functional status. For the analysis of length of stay, we used a negative binomial regression model with a log link, suitable for overdispersed count data. This model facilitated the comparison of the ratio of means both between the prepandemic and pandemic periods and between patients who were COVID-19 positive and those without documented infection during the pandemic.

In our study, we also conducted a sensitivity analysis where we limited our cohort to patients with ICH admitted solely to comprehensive stroke centers. The rationale behind this decision was to control for potential variations in care and outcomes that might be associated with the level of resources and expertise available at different types of hospitals. Comprehensive stroke centers typically have more resources and experienced personnel to deal with complex stroke cases, which could influence patient outcomes.

All analyses used a complete case approach, where study participants with available data for the outcome, exposure, and covariates of interest are included in the analysis. Statistical analyses were conducted using SAS 9.4.

We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines to ensure transparent and complete reporting of our study. To this end, we used the checklists to guide the reporting of our study design, methods, results, and conclusions.[14]

RESULTS

Differences Between Patients With ICH With and Without COVID-19 Infection Admitted During the Pandemic

The first stage of this study, focused on comparing patients with ICH with and without concomitant COVID-19 admitted during the pandemic, evaluated a total of 61 417 patients with ICH (mean age 67.4 [SD 15.3], female sex n=28 923 [46.1%]), including

Downloaded from http://ahajournals.org by on February 1, 2024

1326 with concomitant infection and 60 091 without (Table 1). Compared with patients with ICH who were not infected, those with concomitant infection were younger (65 versus 69 years of age) and more likely to be Black (21 versus 18%) or Hispanic (18 versus 10%, all $P<0.05$; Table 1) (Table S1).

We found evidence of significant differences in outcomes when comparing patients with ICH with and without concomitant COVID-19 infection admitted during the pandemic (Table 2). In unadjusted regression analyses, patients with ICH with versus without concomitant COVID-19 infection had 62% higher odds of poor outcome (odds ratio [OR], 1.62 [95% CI, 1.38–1.92]), 48% higher odds of mortality (OR, 1.48 [95% CI, 1.31–1.67]), and 41% higher odds of being discharged to an SNF/hospice (OR, 1.41 [95% CI, 1.23–1.61]). Similar results were observed in multivariable regression analyses, where patients with ICH with versus without concomitant COVID-19 infection had 68% higher odds of poor outcome (OR, 1.68 [95% CI, 1.40–2.01]), 50% higher odds of mortality (OR, 1.50 [95% CI, 1.33–1.71]), and 66% higher odds of being discharged to an SNF (OR, 1.66 [95% CI, 1.43–1.92]). Sensitivity analyses restricting the study population to 27 943 cases with ICH enrolled at stroke centers (Table S2) yielded similar results for all analyses, including poor outcome (OR, 1.52 [95% CI, 1.13–2.05]), mortality (OR, 1.19 [95% CI, 0.97–1.47]), and discharge to an SNF (OR 1.66 [95% CI, 1.33–2.01]).

Differences Between Patients With ICH Admitted Before and During the Pandemic

The second stage of the present study, focused on comparing ICH cases that took place before and during the COVID-19 pandemic, evaluated a total of 127 424 patients with ICH (mean age 67.7 [SD 15.3], female sex n=59 270 [46.5%]), including 62 743 during the prepandemic period and 64 681 during the pandemic (Table 3). The baseline characteristics of patients with ICH admitted before and during the pandemic were overall similar, despite some statistically significant results expected given the large sample size but which corresponded to small differences (Table 3) (Table S3).

We also found evidence of significant differences in outcomes when comparing patients with ICH admitted before and during the pandemic (Table 4). In unadjusted regression analyses, patients with ICH admitted during versus before the COVID-19 pandemic had 5% higher odds of poor outcome (OR, 1.04 [95% CI, 1.01–1.07]) and lower odds of being discharged to an SNF/hospice (OR, 0.92 [95% CI, 0.88–0.95]). No statistically significant differences were observed in mortality (OR, 1.00 [95% CI, 0.98–1.03]) or discharge. Similar results were observed in multivariable regression analyses that indicated that patients with ICH admitted during versus before the COVID-19 pandemic had 10% higher odds of poor outcome (OR, 1.10 [95% CI, 1.06–1.14]), with no significant changes observed in discharge to an SNF/hospice (OR, 0.90 [95% CI, 0.88–0.92]). In contrast to univariate analyses, multivariable regression demonstrated higher odds of mortality (OR, 1.04 [95% CI, 1.01–1.07]). Sensitivity analyses restricting the study population to 57 787 cases with ICH enrolled at comprehensive stroke centers (Table S4) yielded comparable results, including a significant association for poor outcome (OR, 1.14 [95% CI, 1.08–1.21]) and no statistically significant differences for mortality (OR, 1.03 [95% CI, 0.98–1.07]).

DISCUSSION

This study provides a comprehensive analysis of the consequences of COVID-19 in patients with ICH. We leveraged a large observational data set to investigate 2 key aspects: the outcomes of patients with ICH with and without concomitant COVID-19 infection during the pandemic and a comparison of patients with ICH admitted during similar periods before and during the pandemic. Our findings indicate that patients with ICH who also had COVID-19 had higher risks of poor functional outcomes, death, and discharge to SNFs or hospice. We also observed that patients with ICH admitted during the pandemic had slightly worse outcomes compared with those admitted before the pandemic.

Existing research strongly suggests that COVID-19 infection worsens the outcomes of various cardiovascular diseases, including myocardial infarctions and acute ischemic strokes, with patients infected with COVID-19 experiencing significantly higher mortality rates.[15–18] Furthermore, during the pandemic, preventive measures potentially affected acute ischemic stroke management, leading to treatment delays and subsequently influencing early adverse outcomes in patients with acute ischemic stroke.[19] However, the impact of COVID-19 on hemorrhagic stroke, specifically ICH, is less well studied and primarily derived from smaller, single-center studies.[17,20–22] Similar findings have been reported in our study, further highlighting the devastating impact of the COVID-19 pandemic on health care outcomes. The exact mechanisms behind this observation remain unclear. Specifically, it is not yet known whether these adverse outcomes are attributable to the direct impact of the virus on cerebral vessels or if they are due to the overall effect of the virus on the patient's bodily functions.[23]

We also observed that patients with ICH who were COVID-19 positive were typically younger and more likely to belong to underrepresented racial or ethnic

Downloaded from http://ahajournals.org by on February 1, 2024

Table 1. Description and Comparison of Baseline Characteristics Among Patients With ICH Who Are COVID-19 Positive Compared With Those With No Documented COVID-19 Infection

Variable	Overall 61 417	Positive for COVID-19 N=1326	Negative for COVID-19 N=60 091	*P* value
Patient demographics, n (%)				
Age, y, mean (SD)	67.4 (15.3)	64.1 (15.9)	67.4 (15.2)	<0.0001
Female sex	28 923 (46.1%)	589 (44.4%)	28 334 (46.1%)	0.215
Race or ethnicity				<0.0001
White	37 603 (59.9%)	625 (47.1%)	36 978 (60.2%)	
Black	11 234 (17.9%)	281 (21.1%)	10 953 (17.8%)	
Hispanic	64,42 (10.2%)	244 (18.4%)	6198 (10.1%)	
Asian	33,94 (5.4%)	64 (4.8%)	3330 (5.4%)	
Other	40,44 (6.4%)	112 (8.4%)	3932 (6.4)	
Missing	26 (0.04%)	0 (0.0%)	26 (0.04%)	
Vascular risk factors				
Hypertension Yes	45 683 (73.4%)	970 (73.2%)	44 713 (73.4%)	0.901
Dyslipidemia Yes	24 109 (38.7%)	488 (36.8%)	23 621 (38.7%)	0.154
Diabetes Yes	16 515 (26.5%)	451 (34.0%)	16 064 (26.3%)	<0.0001
Obesity/overweight Yes	18 809 (30.2%)	415 (31.3%)	18 394 (30.2%)	0.370
Smoker Yes	8277 (13.3%)	141 (10.6%)	8136 (13.3%)	0.004
Missing	515 (0.8%)	2 (0.1%)	513 (0.8%)	-
Comorbidities				
Previous stroke/transient ischemic attack Yes	14 818 (23.8%)	314 (23.7%)	14 504 (23.8%)	0.933
Carotid stenosis Yes	1112 (1.7%)	21 (1.5%)	1091 (1.7%)	0.577
Atrial fibrillation/flutter Yes	10 203 (16.4%)	208 (15.7%)	9995 (16.4%)	0.495
Coronary artery disease/prior myocardial infarction Yes	9815 (15.7%)	195 (14.7%)	9620 (15.8%)	0.291
Chronic renal insufficiency Yes	6489 (10.4%)	167 (12.6%)	6322 (10.3%)	0.008
Missing	515 (0.8%)	2 (0.1%)	513 (0.8%)	-
Medications before admission				
Antithrombotic	25 726 (42.1%)	510 (39.0%)	25 216 (42.1%)	0.023
Antiplatelets	18 522 (29.5%)	357 (26.9%)	18 165 (29.5%)	0.036
Anticoagulants	10 712 (17.%)	234 (17.6%)	10 478 (17.0%)	0.574
Antihypertensives	29 480 (46.9%)	647 (48.7%)	28 833 (46.9%)	0.182
Cholesterol reducers	23 484 (37.4%)	476 (35.9%)	23 008 (37.%)	0.244
Diabetes medications	10 826 (17.2%)	298 (22.4%)	10 528 (17.1%)	<0.0001
Missing	1653 (2.6%)	20 (1.5%)	1633 (2.6%)	
Admission vital signs				
Heart rate (30–200), bpm*	84.9 (19.3)	86.2 (19.3)	84.9 (19.3)	0.021
Missing	35.4%	30.0%	35.5%	
Systolic BP (50–250), mm Hg*	163.5 (34.6)	159.3 (35.3)	163.6 (34.6)	<0.0001
Missing	33.3%	28.5%	33.4%	
Diastolic BP (20–200), mm Hg*	91.7 (23.3)	89.3 (23.2)	91.7 (23.3)	0.001

(*Continued*)

Downloaded from http://ahajournals.org by on February 1, 2024

Table 1. Continued

Variable	Overall 61 417	Positive for COVID-19 N=1326	Negative for COVID-19 N=60 091	*P* value
Missing	32.2%	27.6%	32.3%	
Admission laboratory values				
Blood glucose (20–800), mg/dL*	151.60 (68.9)	162.6 (78.2)	151.3 (68.6)	<0.0001
Missing	32.3%	29.0%	32,4%	
Hemoglobin A1c (0–20), %*	6.2 (1.6)	6.7 (2.0)	6.2 (1.6)	<0.0001
Missing	63.8%	59.7%	63.8%	
Low-density lipoprotein (30–500), mg/dL*	94.8 (38.7)	92.9 (36.3)	94.9 (38.7)	0.347
Missing	60.5%	60.3%	60.06%	
Serum creatinine (0–150), mg/dL*	1.4 (4.0)	1.5 (4.3)	1.4 (4.0)	0.065
Missing	35.5%	30.8%	35.6%	
Arrival information				
Off-hour arrival (6 PM to 7 AM)	37 569 (59.8%)	819 (61.7%)	36 750 (59.8%)	0.156
Transferred in from other hospital	23 421 (37.4%)	526 (39.6%)	22 895 (37.%)	0.089
Initial National Institutes of Health Stroke Scale score (0–42)*	11.9 (10.8)	13.9 (10.7)	11.9 (10.8)	<0.0001
Length of stay	9.0 (11.7)	12.8 (14.9)	8.9 (11.6)	<0.0001
Hospital information				
Annual volume of ICH stroke admission	62 742 (7.6%)	1326 (79.7%)	61 416 (76.7%)	
Missing	0	0	0	
Academic hospital	52 175 (84.4%)	1135 (87.1%)	51 040 (84.3%)	0.062
Missing	963 (1.5%)	24 (1.8%)	939 (1.5%)	

BP indicates blood pressure; and ICH, intracerebral hemorrhage. *= mean (SD).

groups, consistent with previous studies on ischemic stroke patients.[24,25] It is important to note that although we observed a higher prevalence of diabetes among patients who were COVID-19 positive, the reasons behind this observation are outside the scope of our current study. Potential explanations such as immune system response, shared risk factors, chronic inflammation, and medication effects could be explored in future research.[26]

Although the primary focus of this study is on the clinical outcomes associated with COVID-19 and ICH, it is important to contextualize our findings within the broader framework of cerebrovascular diseases. Previous literature has elucidated that one of the primary cerebrovascular manifestations of COVID-19 is the promotion of thrombosis, suggesting a procoagulant effect of the virus on the vascular system.[27] This has led to acute ischemic strokes being more

Table 2. Prevalence and Odds Ratios of Outcomes in Patients Who Are COVID-19 Positive Compared With Those With No Documented Infection (Reference)

Stroke outcome at discharge	Model type	No. and (%) available data	Odds ratio	CI
Discharge to skilled nursing facility or hospice	Adjusted*	47 693 (77.65%)	1.66	1.43–1.92
	Unadjusted	49 167 (80.05%)	1.40	1.23–1.60
Length of stay†,*	Adjusted*	58 481 (95.22%)	1.32	1.25–1.39
	Unadjusted	60 278 (98.15%)	1.43	1.35–1.51
High modified Rankin Scale score (4, 5, 6)	Adjusted*	39 668 (64.59%)	1.68	1.40–2.01
	Unadjusted	40 718 (66.30%)	1.62	1.37–1.91
Mortality	Adjusted*†	60 894 (99.15%)	1.50	1.33–1.71
	Unadjusted	61 417 (100.0%)	1.47	1.31–1.66

*The following covariates were used in the adjusted models: age, sex, race or ethnicity, antiplatelet or anticoagulant before admission, hypertension, diabetes, heart failure, coronary artery disease/myocardial infarction, prior stroke, renal insufficiency, atrial fibrillation, smoking, alcohol/drug abuse, sleep apnea, prestroke modified Rankin Scale score, hypertensive, arrival via emergency medical services, arrival on vs off hours, admission National Institutes of Health Stroke Scale score, region, teaching hospital, number of beds, annual stroke volume, rural location, stroke center status.

†The estimate is a relative risk (with its 95% CI), not odds ratio when the outcome is length of stay.

Downloaded from http://ahajournals.org by on February 1, 2024

Table 3. Description and Comparison of Patient Baseline Characteristics Data Among Patients With ICH Who Were Admitted to a Hospital Before the COVID-19 Pandemic and Time-Matched Patients During the COVID-19 Pandemic

Variable	Overall	Before the COVID-19 pandemic	During the COVID-19 pandemic	*P* value
	127 424	62 743	64 681	
Patient demographics				
Age, y, mean (SD)	67.6 (15.3)	68.0 (15.3)	67.3 (15.3)	<0.0001
Female sex	59 270 (46.5%)	30 347 (46.9%)	28 923 (46.1%)	0.003
Race or ethnicity	7861 (6.1%)	3817 (5.9%)	4044 (6.4%)	<0.0001
White	77 146 (60.5%)	39 543 (61.1%)	37 603 (59.9%)	
Black	22 715 (17.8%)	11 481 (17.7%)	11 234 (17.9%)	
Hispanic	12 783 (10.0%)	6341 (9.8%)	6442 (10.2%)	
Asian	6852 (5.3%)	3458 (5.3%)	3394 (5.4%)	
Other	77 146 (60.5%)	39 543 (61.1%)	37 603 (59.9%)	
Missing	67 (0.05%)	41 (0.06%)	26 (0.04%)	
Vascular risk factors				
Hypertension	93 370 (73.7%)	47 687 (74.1%)	45 683 (73.4%)	0.002
Dyslipidemia	48 428 (38.2%)	24 319 (37.8%)	24 109 (38.7%)	<0.0001
Diabetes	33 305 (26.3%)	16 790 (26.1%)	16 515 (26.5%)	0.084
Obesity/overweight	36 251 (28.6%)	17 442 (27.1%)	18 809 (30.2%)	<0.0001
Smoker	16 693 (13.1%)	8416 (13.09%)	8277 (13.3%)	0.264
Missing	897 (0.7%)	382 (0.5%)	515 (0.8%)	
Comorbidities				
Previous stroke/transient ischemic attack	30 728 (24.2%)	15 910 (24.7%)	14 818 (23.8%)	<0.0001
Carotid stenosis	2202 (1.7%)	1090 (1.7%)	1112 (1.7%)	0.212
Atrial fibrillation/flutter	21 132 (16.7%)	10 929 (17.0%)	10 203 (16.4%)	
CAD/Prior MI	20 385 (16.1%)	10 570 (16.4%)	9815 (15.7%)	0.001
Chronic renal insufficiency	12 943 (10.2%)	6454 (10.0%)	6489 (10.4%)	0.022
Missing	897 (0.7%)	382 (0.5%)	515 (0.8%)	
Medications before admission				
Antithrombotic	53 175 (42.8%)	27 449 (43.6%)	25 726 (42.1%)	<0.0001
Antiplatelets	38 667 (30.3%)	20 145 (31.1%)	18 522 (29.5%)	<0.0001
Anticoagulants	21 782 (17.0%)	11 070 (17.1%)	10 712 (17.0%)	0.842
Antihypertensives	60 205 (47.2%)	30 725 (47.5%)	29 480 (46.9%)	0.064
Cholesterol reducers	48 035 (37.7%)	24 551 (37.9%)	23 484 (37.4%)	0.051
Diabetic medications	21 337 (16.7%)	10 511 (16.2%)	10 826 (17.2%)	<0.0001
Missing				
Admission vital signs				
Heart rate (30–200), bpm*	84.4 (19.1)	83.9 (18.9)	84.9 (19.3)	<0.0001
Missing				
Systolic BP (50–250), mm Hg*	163.1 (34.5)	162.6 (34.3)	163.5 (34.6)	<0.0001
Missing				
Diastolic BP (20–200), mm Hg*	91.2 (23.2)	90.7 (23.0)	91.7 (23.3)	<0.0001
Missing				
Admission laboratory values				
Blood glucose (20–800), mg/dL*	150.7 (68.4)	149.8 (67.9)	151.60 (68.9)	<0.0001
Missing				
Hemoglobin A1c (0–20), %*	6.2 (1.6)	6.2 (1.5)	6.2 (1.6)	0.003
Missing				
Low-density lipoprotein (30–500), mg/dL*	94.4 (38.1)	94.1 (37.5)	94.85 (38.7)	0.182

(*Continued*)

Downloaded from http://ahajournals.org by on February 1, 2024

Table 3. Continued

Variable	Overall	Before the COVID-19 pandemic	During the COVID-19 pandemic	*P* value
	127 424	62 743	64 681	
Missing				
Serum creatinine (0–150), mg/dL*	1.4 (3.9)	1.4 (3.9)	1.4 (4.0)	0.001
Missing				
Arrival information				
Off-hour arrival (6 PM to 7 AM)	76 397 (59.9%)	38 828 (60.0%)	37 569 (59.8%)	0.578
Missing				
Transferred in from other hospital	48 024 (37.7%)	24 603 (38.1%)	23 421 (37.4%)	0.013
Missing				
Initial National Institutes of Health Stroke Scale score (0–42)	11.7 (10.8)	11.5 (10.7)	11.9 (10.8)	<0.0001
Missing				
Length of stay	8.8 (11.5)	8.6 (11.3)	9.0 (11.7)	<0.0001
Missing				
Hospital information				
Annual volume of ICH stroke admission	127,42 (77.76%)	64 680 (78.6%)	62 742 (76.8%)	<0.0001
Missing				
Academic hospital	106 564 (84.9%)	54 389 (85.3%)	52 175 (84.4%)	<0.0001
Missing				

BP indicates blood pressure; and ICH, intracerebral hemorrhage.

*The following covariates were used in the adjusted models: age, sex, race or ethnicity, antiplatelet or anticoagulant before admission, hypertension, diabetes, heart failure, coronary artery disease/myocardial infarction, prior stroke, renal insufficiency, atrial fibrillation, smoking, alcohol/drug abuse, sleep apnea, prestroke modified Rankin Scale score, hypertensive, arrival via emergency medical services, arrival on vs off hours, admission National Institutes of Health Stroke Scale score, region, teaching hospital, number of beds, annual stroke volume, rural location, stroke center status.

commonly linked to COVID-19 than hemorrhagic cerebrovascular diseases.[28] Additionally, although studies have shown that COVID-19 can induce ICH, prevalent risk factors play a substantial role in its onset.[20,29]

Our study is unique in that it focuses on patients with ICH during the pandemic, a group that has not been extensively studied in the current literature. However, due to the nature of our data set, we cannot definitively conclude whether the observed outcomes are due to the direct biological effects of COVID-19, the health care system being overwhelmed due to the pandemic, or a combination of both. It is plausible that the severe respiratory disease or acute thromboembolic episodes triggered by accelerated inflammatory responses from COVID-19 could contribute to worse outcomes. Future research could further investigate these possibilities.

Table 4. Prevalence and Odds Ratios of Outcomes During the COVID-19 Pandemic Versus Before (Reference) the Pandemic

Stroke outcome at discharge	Model type	No. and (%) available data	Odds ratio	CI
Discharge to skilled nursing facility or hospice	Adjusted*	97 043 (76.16%)	0.90	0.88–0.92
	Unadjusted	99 884 (78.39%)	0.92	0.89–0.95
Length of stay†,*	Adjusted*	118 964 (93.36%)	1.01	1.00–1.02
	Unadjusted	122 407 (96.0%)	1.04	1.03–1.05
High modified Rankin Scale score (4, 5, 6)	Adjusted*	79 519 (62.41%)	1.10	1.06–1.14
	Unadjusted	81 646 (64.07%)	1.04	1.01–1.07
Mortality	Adjusted*	123 869 (97.21%)	1.04	1.01–1.07
	Unadjusted	127 424 (100.0%)	1.00	0.97–1.03

*The following covariates were used in the adjusted models: age, sex, race or ethnicity, antiplatelet or anticoagulant before admission, hypertension, diabetes, heart failure, coronary artery disease/myocardial infarction, prior stroke, renal insufficiency, atrial fibrillation, smoking, alcohol/drug abuse, sleep apnea, prestroke modified Rankin Scale score, hypertensive, arrival via emergency medical services, arrival on vs off hours, admission National Institutes of Health Stroke Scale score, region, teaching hospital, number of beds, annual stroke volume, rural location, stroke center status.

†The estimate is a relative risk (with its 95% CI), not odds ratio when the outcome is length of stay.

Downloaded from http://ahajournals.org by on February 1, 2024

Strengths of our study are the uniquely large sample size, allowing the appropriate evaluation of clinical and biological differences in these patients; the multiinstitutional design, which increases the generalizability of our findings; and the prespecified data collection strategy, which allows the effective harmonization of data across the multiple institutions involved. We acknowledge several limitations, including potential selection bias due to the specific set of hospitals participating in the GWTG-Stroke program, lack of detailed data on COVID-19 diagnosis and treatment, and potential for residual confounding.

CONCLUSIONS

In conclusion, our study highlights the negative impact of the COVID-19 pandemic on outcomes in patients with ICH. These findings underscore the need for further research to understand the mechanisms driving these outcomes and to develop strategies to improve outcomes for patients with ICH during times of health crisis.

ARTICLE INFORMATION

Received May 15, 2023; accepted January 8, 2024.

Affiliations

Department of Neurology (D.R., A.C.L., C.A.R., L.S., A.d.H., K.N.S., G.J.F.) and Department of Neurosurgery (D.R., C.C.M.), Yale School of Medicine, New Haven, CTDuke Clinical Research Institute, Durham, NC (R.Y., B.A., B.M.G.); Department of Neurology, Duke University School of Medicine, Durham, NC (B.M.G.); Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA (S.R.M.); Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI (M.J.R.); and University of Texas Rio Grande Valley, Valley Baptist Medical Center, Harlingen, TX (A.E.H.).

Acknowledgments

The Get With The Guidelines programs are provided by the American Heart Association. The American Heart Association Precision Medicine Platform (https://precision.heart.org/) was used for data analysis. IQVIA (Parsippany, NJ) serves as the data collection and coordination center.

Sources of Funding

The American Heart Association (AHA)'s suite of registries is funded by multiple industry sponsors. The Get With The Guidelines–Stroke (GWTG-Stroke) program is provided by the AHA/American Stroke Association. GWTG-Stroke is sponsored, in part, by Novartis, Novo Nordisk, AstraZeneca, Bayer, Tylenol, and Alexion, AstraZeneca Rare Disease. D.R. is supported by the AHA. A.C.L. is supported by the AHA Medical Student Research Fellowship. G.J.F. is supported by the National Institutes of Health (NIH) and the AHA. K.N.S. is supported by the NIH.

Disclosures

None.

Supplemental Material

Tables S1–S4.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Sahu KK, Mishra AK, Lal A. Comprehensive update on current outbreak of novel coronavirus infection (2019-nCoV). *Ann Transl Med*. 2020;8:393. doi: 10.21037/atm.2020.02.92
3. Bialek S, Boundy E, Bowen V, Chow N, Cohn A, Dowling N, Ellington S, Gierke R, Hall A, MacNeil J, et al. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–march 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:343–346.
4. Qureshi AI, Baskett WI, Huang W, Shyu D, Myers D, Raju M, Lobanova I, Suri MFK, Naqvi SH, French BR, et al. Acute ischemic stroke and COVID-19: an analysis of 27 676 patients. *Stroke*. 2021;52:905–912. doi: 10.1161/STROKEAHA.120.031786
5. Qureshi AI, Abd-Allah F, Al-Senani F, Aytac E, Borhani-Haghighi A, Ciccone A, Gomez CR, Gurkas E, Hsu CY, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Int J Stroke*. 2020;15:540–554. doi: 10.1177/1747493020923234
6. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. 2020;5:279–284. doi: 10.1136/svn-2020-000431
7. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611–2618. doi: 10.1056/NEJMoa041747
8. Ravindra VM, Grandhi R, Delic A, Hohmann S, Shippey E, Tirschwell D, Frontera JA, Yaghi S, Majersik JJ, Anadani M, et al. A. Impact of COVID-19 on the hospitalization, treatment, and outcomes of intracerebral and subarachnoid hemorrhage in the United States. *PLoS One*. 2021;16:e0248728.
9. Adcock AK, Schwamm LH, Smith EE, Fonarow GC, Reeves MJ, Xu H, Matsouaka RA, Xian Y, Saver JL. Trends in use, outcomes, and disparities in endovascular thrombectomy in US patients with stroke aged 80 years and older compared with younger patients. *JAMA Netw Open*. 2022;5:e2215869. doi: 10.1001/jamanetworkopen.2022.15869
10. Ormseth CH, Sheth KN, Saver JL, Fonarow GC, Schwamm LH. The American Heart Association's Get With The Guidelines (GWTG)-Stroke development and impact on stroke care. *Stroke Vasc Neurol*. 2017;2:94–105. doi: 10.1136/svn-2017-000092
11. Smaha LA. The American Heart Association get with the guidelines program. *Am Heart J*. 2004;148:S46–S48. doi: 10.1016/j.ahj.2004.09.015
12. Howard G, Schwamm LH, Donnelly JP, Howard VJ, Jasne A, Smith EE, Rhodes JD, Kissela BM, Fonarow GC, Kleindorfer DO, et al. Participation in get with the guidelines-stroke and its association with quality of care for Stroke. *JAMA Neurol*. 2018;75:1331–1346. doi: 10.1001/jamaneurol.2018.2101
13. Alger HM, Rutan C, Williams JH, Walchok JG, Bolles M, Hall JL, Bradley SM, Elkind MSV, Rodriguez F, Wang TY, et al. American Heart Association COVID-19 CVD registry powered by Get With The Guidelines. *Circ Cardiovasc Qual Outcomes*. 2020;13:E006967. doi: 10.1161/CIRCOUTCOMES.120.006967
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499. doi: 10.1016/j.ijsu.2014.07.013
15. Majeed H, Gangu K, Shekhar R, Sagheer S, Garg I, Shuja H, Bobba A, Chourasia P, Avula SR, Sheikh AB. Impact of COVID-19 on patients hospitalized with ST-segment elevation myocardial infarction in the United States during the early pandemic: an analysis of outcomes, care delivery, and racial disparities in mortality. *Infectious Disease Reports*. 2023;15:55–65. doi: 10.3390/idr15010006
16. de Havenon A, Ney JP, Callaghan B, Delic A, Hohmann S, Shippey E, Esper GJ, Stulberg E, Tirschwell D, Frontera J, et al. Impact of COVID-19 on outcomes in ischemic stroke patients in the United States. *J Stroke Cerebrovasc Dis*. 2021;30:105535. doi: 10.1016/j.jstrokecerebrovasdis.2020.105535
17. Leasure AC, Khan YM, Iyer R, Elkind MSV, Sansing LH, Falcone GJ, Sheth KN. Intracerebral hemorrhage in patients with COVID-19: an analysis from the COVID-19 cardiovascular disease registry. *Stroke*. 2021;52:e321–e323. doi: 10.1161/STROKEAHA.121.034215
18. Kvernland A, Kumar A, Yaghi S, Raz E, Frontera J, Lewis A, Czeisler B, Kahn DE, Zhou T, Ishida K, et al. Anticoagulation use and hemorrhagic stroke in SARS-CoV-2 patients treated at a New York healthcare system. *Neurocrit Care*. 2021;34:748–759. doi: 10.1007/s12028-020-01077-0

Downloaded from http://ahajournals.org by on February 1, 2024

19. Gu S, Li J, Shen H, Dai Z, Bai Y, Zhang S, Zhao H, Zhou S, Yu Y, Tang W. The impact of COVID-19 pandemic on treatment delay and short-term neurological functional prognosis for acute ischemic stroke during the lockdown period. *Front Neurol*. 2022;13:998758. doi: 10.3389/fneur.2022.998758
20. Daly SR, Nguyen AV, Zhang Y, Feng D, Huang JH. The relationship between COVID-19 infection and intracranial hemorrhage: a systematic review. *Brain Hemorrhages*. 2021;2:141–150. doi: 10.1016/j.hest.2021.11.003
21. McHugh DC, Gershteyn A, Boerman C, Holloway RG, Roberts DE, George BP. Effect of COVID-19 pandemic on outcomes in intracerebral hemorrhage. *PloS One*. 2023;18:e0284845. doi: 10.1371/journal.pone.0284845
22. Schmidbauer ML, Ferse C, Salih F, Klingner C, Musleh R, Kunst S, Wittstock M, Neumann B, Schebesch KM, Bösel J, et al. COVID-19 and intracranial hemorrhage: a multicenter case series, systematic review and pooled analysis. *J Clin Med*. 2022;11:11. doi: 10.3390/jcm11030605
23. Mohamed S, Abd El-Mohsen S, Abo El-Hassan O, AbdElHaffez A, Abd El-Aziz N. Incidence and pathophysiologic mechanisms of stroke in the COVID-19 pandemic: the dilemma. *Egypt J Bronchol*. 2020;14:1–3. doi: 10.1186/s43168-020-00033-y
24. Acosta JN, Leasure AC, Both CP, Szejko N, Brown S, Torres-Lopez V, Abdelhakim S, Schindler J, Petersen N, Sansing L, et al. Cardiovascular health disparities in racial and other underrepresented groups: initial results from the all of us research program. *J Am Heart Assoc*. 2021;10:88–89. doi: 10.1161/JAHA.121.021724
25. Gardener H, Sacco RL, Rundek T, Battistella V, Cheung YK, Elkind MSV. Race and ethnic disparities in stroke incidence in the northern Manhattan study. *Stroke*. 2020;51:1064–1069. doi: 10.1161/STROKEAHA.119.028806
26. Gęca T, Wojtowicz K, Guzik P, Góra T. Increased risk of COVID-19 in patients with diabetes mellitus—current challenges in pathophysiology, treatment and prevention. *Int J Environ Res Public Health*. 2022;19:6555. doi: 10.3390/ijerph19116555
27. Stefanou E, Karvelas N, Bennett S, Kole C. Cerebrovascular manifestations of SARS-CoV-2: a comprehensive review. *Curr Treat Options Neurol*. 2023;25:71–92. doi: 10.1007/s11940-023-00747-6
28. McFadyen JD, Stevens H, Peter K. The emerging threat of (micro) thrombosis in COVID-19 and its therapeutic implications. *Circ Res*. 2020;127:571–587. doi: 10.1161/CIRCRESAHA.120.317447
29. Panagiotis N, Stylianos A, Filioglou D, Ellul J. Intracerebral hemorrhage in COVID-19: a narrative review. *J Clin Neurosci*. 2021;89:271–278. doi: 10.1016/j.jocn.2021.05.019

Downloaded from http://ahajournals.org by on February 1, 2024