Stroke

RESEARCH LETTER

Intracerebral Hemorrhage in Patients With COVID-19

An Analysis From the COVID-19 Cardiovascular Disease Registry

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Spontaneous intracerebral hemorrhage (ICH) is a devastating consequence of coronavirus disease 2019 (COVID-19) infection.[1,2] Prior single-center studies have reported ICH in patients with COVID-19, but these findings have not been confirmed in a multicenter study.[3,4]

We sought to describe the prevalence of ICH among hospitalized patients with COVID-19 in the American Heart Association COVID-19 Cardiovascular Disease registry and compare the clinical characteristics and outcomes of COVID-19 patients with and without ICH.

METHODS

Data are available from the American Heart Association after approval of a research proposal (www.heart.org/qualityresearch). We performed a retrospective, cross-sectional analysis of patients enrolled in the American Heart Association COVID-19 Cardiovascular Disease registry.[5] This registry includes consecutive patients ≥18 years old hospitalized with COVID-19 from March 2020 to December 2020 at 107 US hospitals. Patients were enrolled without consent through the Common Rule or through an institutional review board authorization/exemption waiver. Presence of ICH was recorded on the registry case report form. Mortality was defined as either in-hospital death or discharge to hospice. We report descriptive statistics of those with and without ICH. Statistical comparisons were not performed due to the small number of patients with ICH.

RESULTS

This release of the COVID-19 registry included 21 483 patients, of which 48 (0.2%) had an ICH. COVID-19 was diagnosed before ICH in 26 patients, on the same day as ICH in 10 patients, and during hospitalization for ICH in 6 patients. Compared with patients without ICH, those with ICH were nominally older (65 versus 61 years), predominantly male (73% versus 54%), and had more vascular risk factors (Table).

During hospitalization, 75% of patients with ICH received anticoagulation compared with 57% of patients without ICH. Patients with ICH had higher levels of inflammatory markers at admission; were more likely to require intensive care (90% versus 30%), mechanical ventilation (77% versus 19%), and extracorporeal membranous oxygenation (4% versus 0.6%); and had a higher mortality (48% versus 18%) than those without ICH (Table). Of the patients with ICH who died, 15 were diagnosed with COVID-19 before ICH.

DISCUSSION

We report characteristics of ICH in over 21 000 hospitalized patients with COVID-19 from the American Heart Association COVID-19 Cardiovascular Disease registry. We found that ICH was rare among hospitalized patients with COVID-19 and that patients with ICH had higher mortality than those without ICH. We also observed greater

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Table. Clinical Characteristics of COVID-19 Positive Patients With and Without ICH

Baseline characteristics	Patients without ICH (N=21 483)	Patients with ICH (N=48)
Patient demographics		
Age, y, mean±SD	61.2±17.9	64.8±12.7
18–45 y	4368/21 483 (20.3%)	4/48 (8.3%)
46–64 y	7373/21 483 (34.3%	14/48 (29.2%)
65 +	9742/21 483 (45.4%)	30/48 (62.5)
Female sex, %	9871/21 483 (45.9%)	13/48 (27.0%)
Race/ethnicity, %		
Non-Hispanic White	8184/21 483 (38.1%)	19/48 (39.6%)
Non-Hispanic Black	5522/21 483 (25.7%)	10/48 (20.8%)
Hispanic	5466/21 483 (25.4%)	12/48 (25%)
Asian	854/21 483 (4.0%)	4/48 (8.3%)
Other/undetermined	1351/21 483 (6.2%)	3/48 (6.3%)
Medical history, %		
Atrial fibrillation/flutter	1997/21 483 (9.3%)	5/48 (10.4%)
Previous stroke/TIA	2437/21 483 (11.3%)	5/48 (10.4%)
CAD/prior MI	1195/21 483 (5.5%	4/48 (8.3%)
Diabetes mellitus	7591/21 483 (35.3%)	23/48 (47.9%)
Hypertension	12 640/21 483 (58.9%)	35/48 (72.9%)
Smoker	1406/21 483 (6.5%)	1/48 (2.1%)
Dyslipidemia	7402/21 483 (34.4%)	22/48 (45.8%)
Heart failure	2496/21 483 (11.6%)	4/48 (8.3%)
Pulmonary disease	4012/21 483 (18.7%)	4/48 (8.3%)
Chronic kidney disease	2778/21 483 (12.9%)	6/48 (12.5%)
Medications before admission, %		
Antihypertensive	11 119/21 043 (52.84%)	29/46 (63.0%)
Antiplatelet	5804/21 413 (27.1%)	15/48 (31.2%)
Anticoagulant	2957/21 043 (14.1%)	7/46 (15.2%)
Statin	7773/8035 (96.7%)	21/26 (95.4%)
COVID-19 diagnosis, %		
Before admission	7330/21 428 (34.2%)	17/48 (35.4%)
During admission	13 665/21 428 (63.8%)	30/48 (62.5%)
After admission	341/21 428 (1.6%)	0/48
Unknown	92/21 428 (0.4%)	1/48 (2.1%)
Presenting symptoms, %		
Fever	11 844/21 297 (55.6%)	23/48 (47.9%)
Cough/shortness of breath	11 951/21 297 (56.1%)	24/48 (50%)
Headache	2013/21 297 (9.5%)	7/48 (14.6%)
Nausea/vomiting	5812/21 297 (27.3%)	10/48 (20.8%)
Loss of smell/taste	983/21 297 (4.6%)	1/48 (2.1%)
Altered mental status	2217/21 297 (10.4%)	8/48 (16.7%)
Hospital course, %		
ICU care	6562/21 382 (30.7%)	43/48 (89.6%)
Mechanical ventilation	4115/21 378 (19.2%)	37/48 (77.1%)
ECMO	131/21 368 (0.6%)	2/48 (4.2%)
Admission labs, median (IQR)		
Hemoglobin, g/dL	13.0 (11.4–14.3)	13.3 (10.9–14.1)
WBC, K/μL	7.0 (5.1–9.7)	10.4 (7.7–12.7)
Platelets, g/dL	204.0 (157.0–266.0)	222.5 (157–290)
Creatinine, mg/dL	1 (0.8–1.47)	1.05 (0.89–1.5)
Ferritin, ng/mL	561.4 (248.8–1156.0)	910 (324.2–1457.5)
CRP, mg/L	19.1 (7.0–85.6)	16.1 (6.2–79.7)
IL-6, pg/mL	18 (5.0–58.0)	127.1 (3.9–158)
Medications during admission, %		
Anticoagulation	12 223/21 483 (56.9%)	36/48 (75.0%)
Convalescent serum	1570/21 023 (7.5%)	8/48 (16.7%)
Hydroxychloroquine	7206/21 368 (33.72%)	13/48 (27.1%
Remdesivir	3227/21 383 (15.1%)	12/48 (25%)
Tocilizumab	1653/21 382 (7.7%)	40/48 (83.3%)
In-hospital mortality or discharge to hospice, %	3946 /21 483 (18.4%)	23/48 (47.9%)

CAD indicates coronary artery disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECMO, extracorporeal membranous oxygenation; ICH, intracerebral hemorrhage; ICU, intensive care unit; IL-6, interleukin 6; IQR, interquartile range; MI, myocardial infarction; TIA, transient ischemic attack; and WBC, white blood cell count.

use of anticoagulation in patients with versus without ICH, supporting the findings of early single-center studies of ICH in COVID-19 in the New York City health system.[1,4]

Although this is the first multicenter study of ICH in COVID-19, there are limitations. First, we describe the prevalence of ICH only among patients hospitalized with COVID-19; prevalence may differ among patients who did not seek or require hospital-based care for COVID-19. Second, reporting hospitals may not be representative of all US hospitals. Third, we lacked detailed data on the timing of ICH relative to hospital admission, COVID-19 diagnosis, and anticoagulation and lacked a control group for comparison. We are, therefore, unable to make causal assumptions about COVID-19 and ICH. Fourth, we lacked data on the location and severity of ICH. Fifth, the small number of patients with ICH precluded statistical analyses. ICH may have been under-ascertained in the registry, as many patients hospitalized with COVID-19 may not have had neuroimaging to detect an ICH.

In summary, our findings suggest that ICH is rare among patients hospitalized for COVID-19. While mortality in ICH is typically high, it may be higher than expected in ICH patients with COVID-19. Further studies are needed to determine the risk, predictors, and outcomes of ICH during COVID-19, particularly among patients who are treated with anticoagulation.

ARTICLE INFORMATION

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REFERENCES

1. Melmed KR, Cao M, Dogra S, Zhang R, Yaghi S, Lewis A, Jain R, Bilaloglu S, Chen J, Czeisler BM, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. *J Thromb Thrombolysis*. 2021;51:953–960. doi: 10.1007/s11239-020-02288-0
2. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol*. 2020;77:1018–1027. doi: 10.1001/jamaneurol.2020.2065
3. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, Lewis A, Melmed K, Hochman K, Horwitz L, et al. Hemorrhagic stroke and anticoagulation in COVID-19. *J Stroke Cerebrovasc Dis*. 2020;29:104984. doi: 10.1016/j.jstrokecerebrovasdis.2020.104984
4. 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*. 2020:1–12. doi: 10.1007/s12028-020-01077-0
5. Alger Heather M, Rutan Christine, Williams Joseph H, Walchok Jason G, Bolles Michele, Hall Jennifer L, Bradley Steven M, Elkind Mitchell S.V, Rodriguez Fatima, Wang Tracy Y, et al. American heart association COVID-19 CVD registry powered by get with the guidelines. *Circulation: Cardiovascular Quality and Outcomes*. 2020;13:e006967.