Increased stroke severity and mortality in patients with SARS-CoV-2 infection: An analysis from the N3C database

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Background: Studies from early in the COVID-19 pandemic showed that patients with ischemic stroke and concurrent SARS-CoV-2 infection had increased stroke severity. We aimed to test the hypothesis that this association persisted throughout the first year of the pandemic and that a similar increase in stroke severity was present in patients with hemorrhagic stroke. *Methods:* Using the National Institute of Health National COVID Cohort Collaborative (N3C) database, we identified a cohort of patients with stroke hospitalized in the United States between March 1, 2020 and February 28, 2021. We propensity score matched patients with concurrent stroke and SARS-COV-2 infection and available NIH Stroke Scale (NIHSS) scores to all other patients with stroke in a 1:3 ratio. Nearest neighbor matching with a caliper of 0.25 was used for most factors and exact matching was used for race/ethnicity and site. We modeled stroke severity as measured by admission NIHSS and the outcomes of death and length of stay. We also explored the temporal relationship between time of SARS-COV-2 diagnosis and incidence of stroke. *Results:* Our query identified 43,295 patients hospitalized with ischemic stroke (5765 with SARS-COV-2, 37,530 without) and 18,107 patients hospitalized with hemorrhagic stroke (2114 with SARS-COV-2, 15,993 without). Analysis of our propensity matched cohort revealed that stroke patients with concurrent SARS-COV-2 had increased NIHSS (Ischemic stroke: IRR=1.43, 95% CI:1.33−1.52, $p<0.001$; hemorrhagic stroke: IRR=1.20, 95% CI:1.08−1.33, $p<0.001$), length of stay (Ischemic stroke: estimate = 1.48, 95% CI: 1.37, 1.61, $p<0.001$; hemorrhagic stroke: estimate = 1.25, 95% CI: 1.06, 1.47, $p=0.007$) and higher odds of death (Ischemic stroke: OR 2.19, 95% CI: 1.79−2.68, $p<0.001$; hemorrhagic stroke: OR 2.19, 95% CI: 1.79−2.68, $p<0.001$). We observed the highest incidence of stroke diagnosis on the same day as SARS-COV-2 diagnosis with a logarithmic decline in counts. *Conclusion:* This retrospective observational analy-

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Received May 17, 2022; revision received January 6, 2023; accepted January 9, 2023.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.106987

sis suggests that stroke severity in patients with concurrent SARS-COV-2 was increased throughout the first year of the pandemic.
Keywords: Stroke—Ischemic stroke—Hemorrhagic stroke—SARS-CoV-2—COVID-19—NIHSS

Introduction

Infection with SARS-CoV-2 is associated with neurological and cerebrovascular complications.[1, 2, 3] Additionally, several studies found greater stroke severity in patients with ischemic stroke (IS) and concurrent SARS-CoV-2 infection.[4, 5, 6, 7, 8, 9] Most of these data come from the early COVID-19 pandemic period when there was rapid and substantial disruption of stroke care delivery and resources.[10, 11, 12, 13, 14, 15] Additionally, several observational studies investigating the effect of COVID-19 on ischemic stroke severity and recovery come from single center studies with relatively low sample sizes of SARS-CoV-2 positive patients.[1,7,8] This leads to limited generalizability and uncertainty of the magnitude of COVID-19's effect on IS populations remains unclear. The same is true for hemorrhagic stroke (HS), which has even less published literature and smaller sample sizes.

By using the National Institute of Health (NIH) National COVID Cohort Collaborative (N3) database, we tested the hypotheses that 1) a concurrent SARS-CoV-2 infection with an acute stroke causes greater severity of stroke deficits as measured by the NIH stroke scale throughout the first year of the pandemic, and 2) a concurrent SARS-CoV-2 infection with an acute HS causes greater severity of stroke deficits as measured by the NIH stroke scale throughout the first year of the pandemic.

Methods

Patients

We performed a query of the National Institute of Health (NIH) National COVID Cohort Collaborative (N3C) limited data set to identify patients aged 18 or older who were hospitalized in the United States for IS or HS (including non-traumatic subarachnoid hemorrhage) between March 1, 2020 and February 28, 2021. The N3C database is compiled by a community of healthcare systems that report electronic health record information from patients with positive SARS-CoV-2 tests and a random sampling of controls (negative SARS-CoV-2 tests) at the same time point in a 1 to 2 ratio.[16] N3C controls are matched with positive SARS-CoV-2 tests on age group, sex, race, and ethnicity during the sampling process. We collected person-level data on all acute stroke hospitalizations. We defined a stroke hospitalization as any documented stroke diagnosis occurring within a time period of one week before or up to six weeks after any hospital admission, but before discharge. We defined a patient as having concurrent stroke and SARS-CoV-2 infection by any coded stroke diagnoses recorded within a timeframe of one week before or up to 3 months after a positive PCR or antigen SARS-CoV-2 test. Patients were defined as non-concurrent if they did not have an acute stroke hospitalization within the one week before to three months after positive PCR or antigen test for SARS-CoV-2. The time frame from one week prior up to three months post positive PCR or antigen test increased the likelihood that we captured acute stroke diagnoses with concurrent SARS-CoV-2 from early infection manifestation to longer term infection effects; this was critical in order to investigate the main effect of COVID-19 encompassing time-varying stroke risk during early to late infection time courses. All individual patient medial record information from the time of indexed acute stroke diagnosis to August 24, 2021 were available. This closed the study's observation time period on the right.

Demographics, characteristics and outcomes

Data on age in years, sex, race/ethnicity, presence pre-existing medical comorbidities, admission NIH stroke scale (NIHSS) total scores, length of stay in days, and incident death. Codesets used in our data pipeline are available in Table S1. Fields with counts between 0 and 20 patients were censored per N3C regulations to protect anonymity.

Statistical methods

Initial unadjusted comparisons between concurrent SARS-CoV-2 infection and non-concurrent for both stroke groups used Fisher's exact tests or Wilcoxon rank sum tests. Propensity score matching was used to balance the covariates between concurrent and non-concurrent groups for both ischemic and hemorrhagic stroke diagnoses limited to patients documented NIHSS scores at admission. We employed matching at a 1:3 concurrent SARS-CoV-2 infection to non-concurrent patient ratio with exact matching for race/ethnicity and N3C data partner site. We utilized nearest neighbor matching with a caliper of 0.25 for other clinical and demographic factors including premorbid obesity, Diabetes Mellitus II (DM), Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), Peripheral Vascular Disease (PVD), Myocardial Infarction (MI), End-Stage Renal Disease (ESRD), sex, and age. We calculated standardized differences before and after matching for these clinical variables as seen in Table 1. See Fig. 1 for a flow diagram

depicting identification of ischemic and hemorrhagic stroke cohorts and their respective concurrent SARS-CoV-2 infection and non-concurrent strata used for descriptive statistics and propensity score matching analysis.

In the matched cohort, NIHSS scores on admission were compared between concurrent SARS-CoV-2 infection and non-concurrent groups using Poisson regression with an unstructured correlation matrix within matched sets to calculate the incidence rate ratio (IRR). A Poisson distributional assumption best reflected the observed right-skewed count data. Concurrent vs non-concurrent group differences in mortality (as documented in the N3C database prior to data query) were assessed with a conditional logistic regression model, while time from stroke hospitalization until death used a stratified Cox proportional hazard model with strata defined by matched set. We used a generalized linear model, with hospital length of stay log transformed (LOS) and an unstructured correlation matrix within matched sets, to assess concurrent and non-concurrent group differences in hospital LOS for survivors only. All analyses were performed using R version 3.5.1. Access to code utilized in this study and the underlying data can be granted on an individual basis to individuals who join N3C and join our project workspace.

Results

Patient demographics and characteristics

Our query identified 61,402 hospitalizations for stroke in the N3C database from March 1, 2020 to February 28, 2021. There were 5765 IS patients with concurrent SARS-COV-2 and 37,530 without. IS patients with concurrent SARS-COV-2 were slightly older (mean (SD) age 67.9 (14.7) years vs 67.0 (15.4) years, p <0.001), more frequently Black or African American, Latino, or Asian (24.4% vs 21.5%, 14.4% vs 7.4%, and 3.6% vs 2.3% respectively, p <0.001), and more likely to be male (55.8% vs 52.5% p < 0.001). Regarding vascular risk factors, patients with concurrent SARS-COV-2 were more likely to have DM or ESRD prior to their stroke (55.1% vs 44.4% and 8.7% vs 5.8% respectively, p < 0.001). There were no differences observed in PVD, MI, CHF, or obesity as shown in Table 1. Propensity score matching of IS patients with documented admission NIHSS yielded a sample of 841 concurrent SARS-COV-2 patients and 2402 matched non-concurrent stroke patients. Standardized differences of baseline clinical covariates were well within acceptable limits.

We identified 2114 (13.2%) HS hospitalizations with concurrent SARS-COV-2 infection and 15,993 without. Age was similar between concurrent and non-concurrent HS groups. Patients with HS with concurrent SARS-COV-2 were more frequently Latino (16.8% vs 8.5%) and Asian (4.4% vs 3.2%) p <0.001. They were also more frequently male (60.9% vs 55.7% p < 0.001). HS patients with concurrent SARS-COV-2 more frequently had DM (47.7% vs 36.7% p < 0.001), ESRD (8.2% vs 4.4% p < 0.001), and MI (16.2% vs 13.3% p < 0.001) and less frequently had COPD (9.6% vs 11.9% p = 0.0015). No significant differences in premorbid DM, CHF, peripheral vascular disease, and obesity were observed between these cohorts. See Table 2 for a full description of the HS cohort. Propensity matching of HS patients yielded a sample of 237 concurrent and 647 non-concurrent patients.

Rates of missing NIHSS differed between patients with and without concurrent SARS-COV-2 (greater in concurrent patients) (IS 84.7% vs 71.9% and HS 82.3% vs 87.6%). Sex had less missing data (IS concurrent: <20 patients, IS non-concurrent: 20%, HS concurrent <20 patients, HS non-concurrent 0.6%). Rates of unknown race and ethnicity are included in Table 1.

Temporal analysis of SARS-COV-2 infection and stroke diagnosis

In the IS concurrent group, 2980 of 5765 (51.7%) were diagnosed with SARS-COV-2 infection and IS on the same day. Increased incidence of IS was observed during the first 15 days following a positive SARS-CoV-2 test, with rates of stroke decreasing and ultimately stabilizing after 40 days. We observed a similar trend in HS patients (Fig. 2).

Stroke severity

In the unmatched cohort of IS patients with available admission NIHSS scores (882 concurrent SARS-COV-2 infection and 10551 non-concurrent), median stroke severity was greater in patients with concurrent SARS-COV-2 infection (median (IQR) 9 (3.0, 18.0) vs. 5 (2.0, 12.0) p < 0.001). Modeling of the matched IS sample found a higher mean NIHSS severity score in concurrent SARS-COV-2 patients compared to non-concurrent SARS-COV-2 patients (IRR=1.43, 95% CI:1.33−1.52, p <0.001) (Table 2). Median NIHSS was higher in IS patients with concurrent SARS-COV-2 in the propensity matched sample during every 2-month epoch of the period studied (Fig. 3a).

In the unmatched cohort of HS patients with available admission NIHSS scores (263 concurrent SARS-COV-2 and 2830 non-concurrent), median stroke severity was also greater in patients with concurrent SARS-COV-2 (median (IQR) 15 (5.0, 23.0) vs. 10 (3.0, 18.0) p < 0.001). A Poisson regression model in the matched HS sample found a higher mean NIHSS severity score in concurrent SARS-COV-2 patients versus similar SARS-COV-2 negative patients (IRR=1.20, 95% CI:1.08−1.33, p <0.001). Median NIHSS was higher in HS patients with concurrent SARS-COV-2 in the propensity matched sample during every 2-month epoch of the period studied except March and April, 2020 (Fig. 3b).

Length of stay and death

Patients with IS and concurrent SARS-COV-2 had a longer LOS (median (IQR) 10 (5, 22) days vs 6 (3, 13)

Table 1. *Demographics, Stroke Severity, and Outcome in IS and HS patients with and without concurrent SARS-COV-2 infection. Standardized differences and p-values are shown only for matching variables.*

	Ischemic Stroke							Hemorrhagic Stroke						
						Standardized Differences							Standardized Differences	
	Concurrent (n=5765)		Non-concurrent (n=37,530)		p-value	Before Matching	After Matching	Concurrent (n=2114)		Non-concurrent (n=15,993)		p-value	Before matching	After matching
Age in years[1]	69	(59−78)	68	(58−78)	<0.001	0.062	0.042	63 (51.0, 73.0)	(51−73)	63	(50−75)	0.498	0.015	0.031
Female[2]	2544	(44.1%)	17753	(47.3%)	<0.001	0.059	0.036	822	(38.9%)	6976	(43.6%)	<0.001	0.078	0.008
Race[2]					<0.001	0.35	0.067					<0.001	0.358	0.121
Asian	205	(3.6%)	872	(2.3%)				94	(4.4%)	510	(3.2%)			
African American	1407	(24.4%)	8083	(21.5%)				378	(17.9%)	2874	(18%)			
Hispanic or Latino	831	(14.4%)	2778	(7.4%)				355	(16.8%)	1363	(8.5%)			
Other	30	(0.5%)	122	(0.3%)				997	(47.2%)	9905	(61.9%)			
Caucasian	2647	(45.9%)	23048	(61.4%)				20	(0.9%)	68	(0.4%)			
Unknown	645	(11.2%)	2627	(7.0%)				270	(12.8%)	1273	(8.0%)			
Comorbidities[2]														
DM	3175	(55.1%)	16667	(44.4%)	<0.001	0.215	0.007	1009	(47.7%)	5871	(36.7%)	<0.001	0.225	0.002
CHF	1682	(29.2%)	11097	(29.6%)	0.556	0.009	0.033	501	(23.7%)	3366	(21.0%)	0.006	0.064	0.044
COPD	800	(13.9%)	6137	(16.4%)	<0.001	0.069	0.007	203	(9.6%)	1909	(11.9%)	0.002	0.075	0.012
PVD	760	(13.2%)	5249	(14.0%)	0.102	0.023	0.01	182	(8.6%)	1396	(8.7%)	0.902	0.004	0.039
MI	1119	(19.4%)	7067	(18.8%)	0.295	0.015	0.029	343	(16.2%)	2135	(13.3%)	0.004	0.081	0.048
ESRD	500	(8.7%)	2158	(5.8%)	<0.001	0.113	0.043	174	(8.2%)	705	(4.4%)	<0.001	0.158	0.063
Obesity	1582	(27.4%)	10193	(27.2%)	0.656	0.006	0.002	534	(25.3%)	3831	(24.3%)	0.194	0.03	0.05
Stroke Severity														
Admission Total NIHSS[1]	9.0	(3−18)	5.0	(2−12)				15.0	(5−23)	10.0	(3−18)			
Outcome														
Length of Stay in days[1]	10.0	(5−22)	6.0	(3−13)				14.0	(6−29)	9.0	(4−19)			
Death[2]	1505	(26.1%)	5663	(15.1%)				790	(36.0%)	3519	(22.0%)			

Non-concurrent refers to patients with acute stroke hospitalization that did not have a SARS-CoV-2 infection within the concurrent time frame.
[1]Median (IQR); Wilcoxon Rank Sum test used for between group comparisons
[2]N (%); Fisher's exact test used for between group comparisons [3]Concurrent refers to a positive PCR or antigen test for SARS-CoV-2 infection from 1 week prior to 6 months after the time of acute stroke hospitalization.

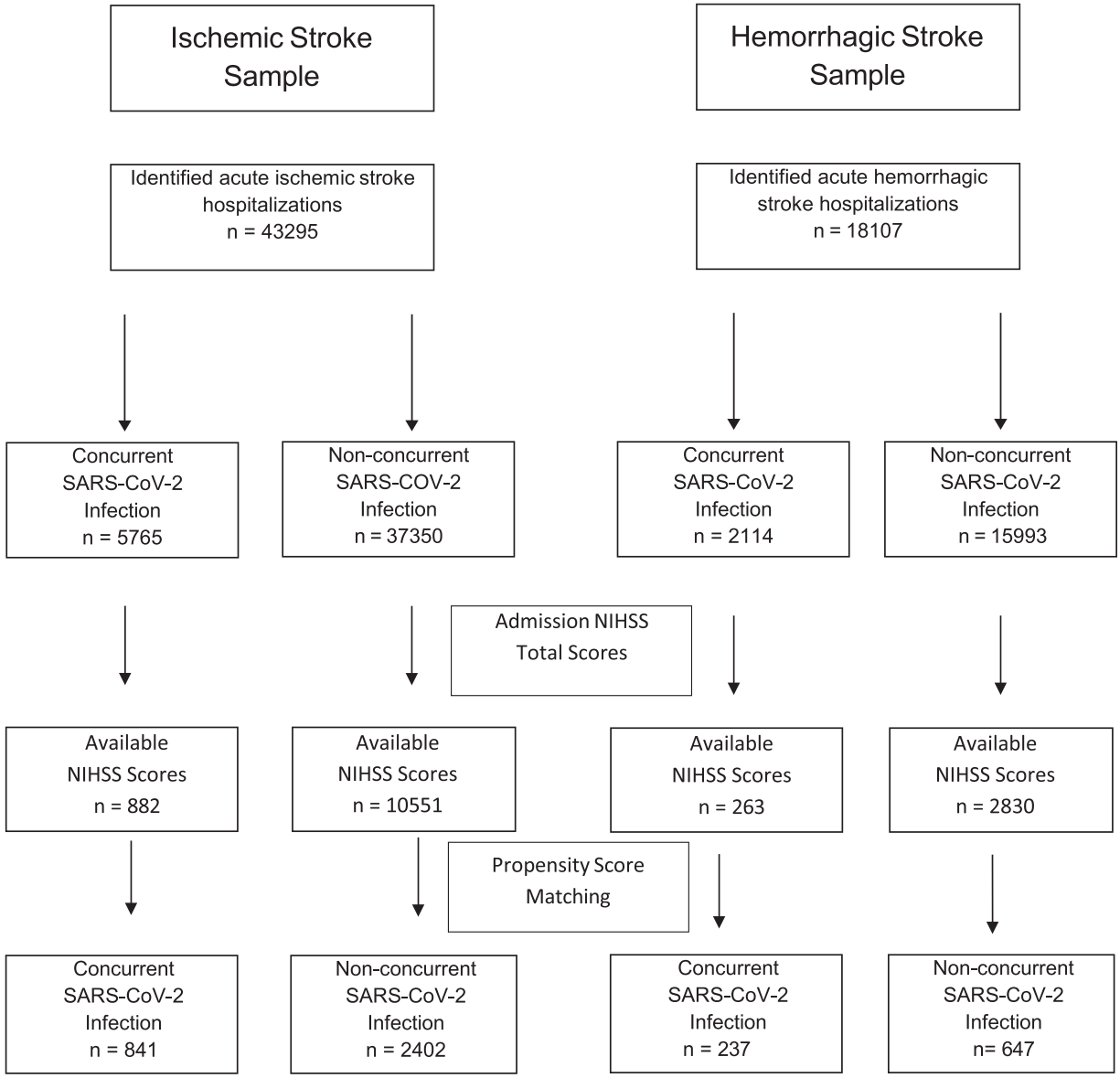

Fig. 1. *A flow diagram depicting ischemic and hemorrhagic stroke cohort identification, amount of patients with NIHSS on admission, and final sample sizes after propensity score matching.*

days, $p < 0.001$). Patients with concurrent SARS-COV-2 had higher mortality (26.1% vs 15.1% $p < 0.001$). In the matched sample, conditional logistic regression estimated that concurrent SARS-COV-2 IS patients had approximately twice the odds of death (OR 2.19, 95% CI: 1.79−2.68, p <0.001). The Cox model for time to death in the matched sample indicated that the concurrent SARS-COV-2 IS patients had a 1.5 times higher hazard of death compared to non-concurrent IS patients (HR=1.51, 95% CI: 1.21, 1.89, p<0.001). In survivors in this sample, the generalized linear model estimated concurrent IS patients had 1.5 times longer LOS compared to non-concurrent IS patients ($e^{(beta)}$ = 1.48, 95% CI: 1.37, 1.61, p <0.001).

Patients with HS and concurrent SARS-COV-2 had a longer LOS (median (IQR) 14 (6, 29) days vs 9 (4, 19) days, $p <$ 0.001) in the entire cohort. Patients with concurrent SARS-COV-2 were more likely to die (36.0% vs 22.0%, $p < 0.001$). In the matched sample, logistic regression estimated that concurrent SARS-COV-2 was associated with just over twice the odds of death (OR=2.05, 95% CI: 1.4−2.87, p<0.001), while the Cox model found no difference in time to death (HR=1.31, 95% CI: 0.94, 1.82, p-value = 0.11). In survivors, the model estimated a 25% longer LOS for concurrent SARS-COV-2 patients compared to non-concurrent SARS-COV-2 patients with hemorrhagic stroke (Estimate = 1.25, 95% CI: 1.06, 1.47, p=0.007).

Discussion

In this large sample of patients from the NIH N3C data repository, we found that both IS and HS severity as

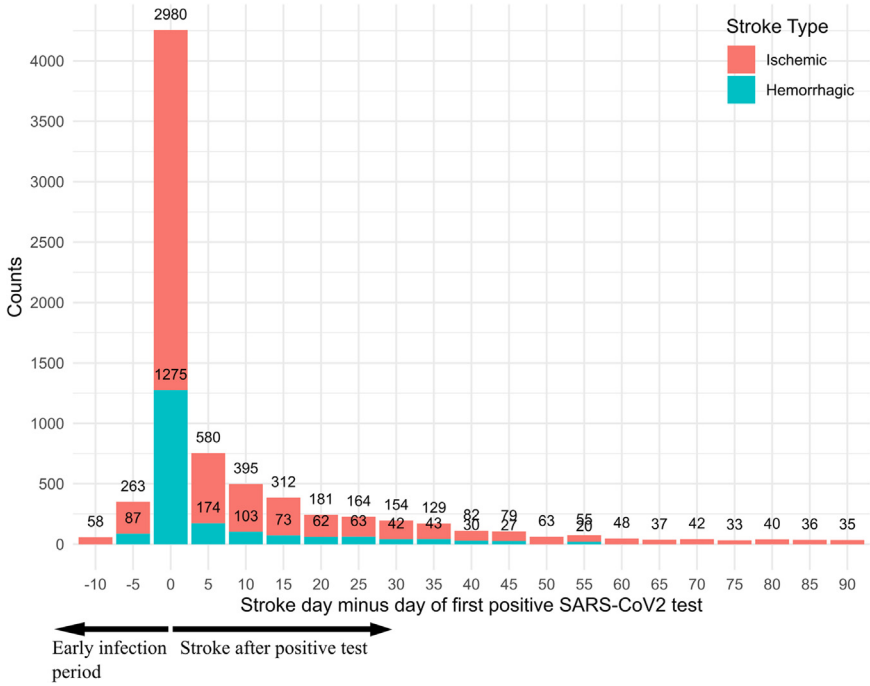

Fig. 2. *Temporal relationship between positive SARS-COV-2 test and stroke diagnosis in our "concurrent SARS-COV-2" population. The Y axis is the count of patients for a given time relationship. The X axis is the difference in days between stroke diagnosis and positive SARS-CoV-2 test, with counts left of zero representing stroke prior to positive test (allowing for fact that infections begin some days prior to first positive test) and the right side representing stroke after positive test. Counts less than 20 are censored to 0. This chart shows that the majority of the strokes in this group occurred within a few weeks of the positive test, with the temporal effect decreasing with time after infection.*

measured by NIHSS was greater in patients with concurrent SARS-COV-2 throughout the entire first year of the pandemic. The association of increased ischemic stroke severity and SARS-COV-2 infection has been observed in previous studies.[4, 5, 6, 7, 8, 9] However, prior analyses were limited to the early period of the pandemic or by comparison to historical controls. Additionally, previous studies of HS and SARS-COV-2 infection have been mostly limited to small samples from single centers.

SARS-COV-2 infection might result in increased stroke severity for several reasons. Reports in the literature suggest a biological link between SARS-COV-2 infection and severe stroke due to viral endothelitis and immunothrombosis.[17, 18, 19] COVID-19 might affect stroke occurrence or severity through an associated systemic coagulopathy or endothelial cell-activating prothrombotic antibodies.[20, 21] Additionally, this observed increase in stroke severity measured by NIHSS may be related to the effects of systemic illness in the setting of COVID-19. A third possibility would be that there were differences between patients with and without COVID-19 due to alterations in stroke systems of care. However, our data demonstrates that this disparity in stroke severity and outcome continued throughout the pandemic even as stroke care utilization normalized. Finally, patient specific differences may exist between those with and without COVID-19. We addressed this possibility with a propensity score analysis that matched for clinical and demographic factors. Matching by site further mitigates the potential of confounding by the effects of illness trends in hospitals intermittently overwhelmed by COVID-19.

In addition to stroke severity, we also investigated important stroke outcomes including death and length of stay. Our study confirms what other studies have found; increased mortality in patients with both IS and HS with concurrent SARS-COV-2 infection.[4, 7, 15, 22, 23, 24, 25]

Demographically, we found that the concurrent SARS-COV-2 IS group had more Hispanic or Latino, Black/African American Non-Hispanic, and Asian Non-Hispanic patients than the non-concurrent group. A previous study found racial disparity in the prevalence of stroke in SARS-COV-2 patients with a skew towards a higher rate of non-White patients with SARS-COV-2 having IS.[26] While our study identifies higher proportions of Hispanic or Latino and Black/African American Non-Hispanic patients in the concurrent group, the structure of the N3C database matches SARS-CoV-2 infection cases and control (non-SARS-COV-2 infected patients) based on a 1:2 ratio for age group, sex, race, and ethnicity upon entry to the database from each participating site. This prevents us from drawing conclusions about the demographic differences in the US stroke population in general. Further study is needed to assess racial disparities in stroke prevalence, severity, and outcome.

Most patients with stroke and concurrent SARS-COV-2 infection were diagnosed with stroke on the same day as

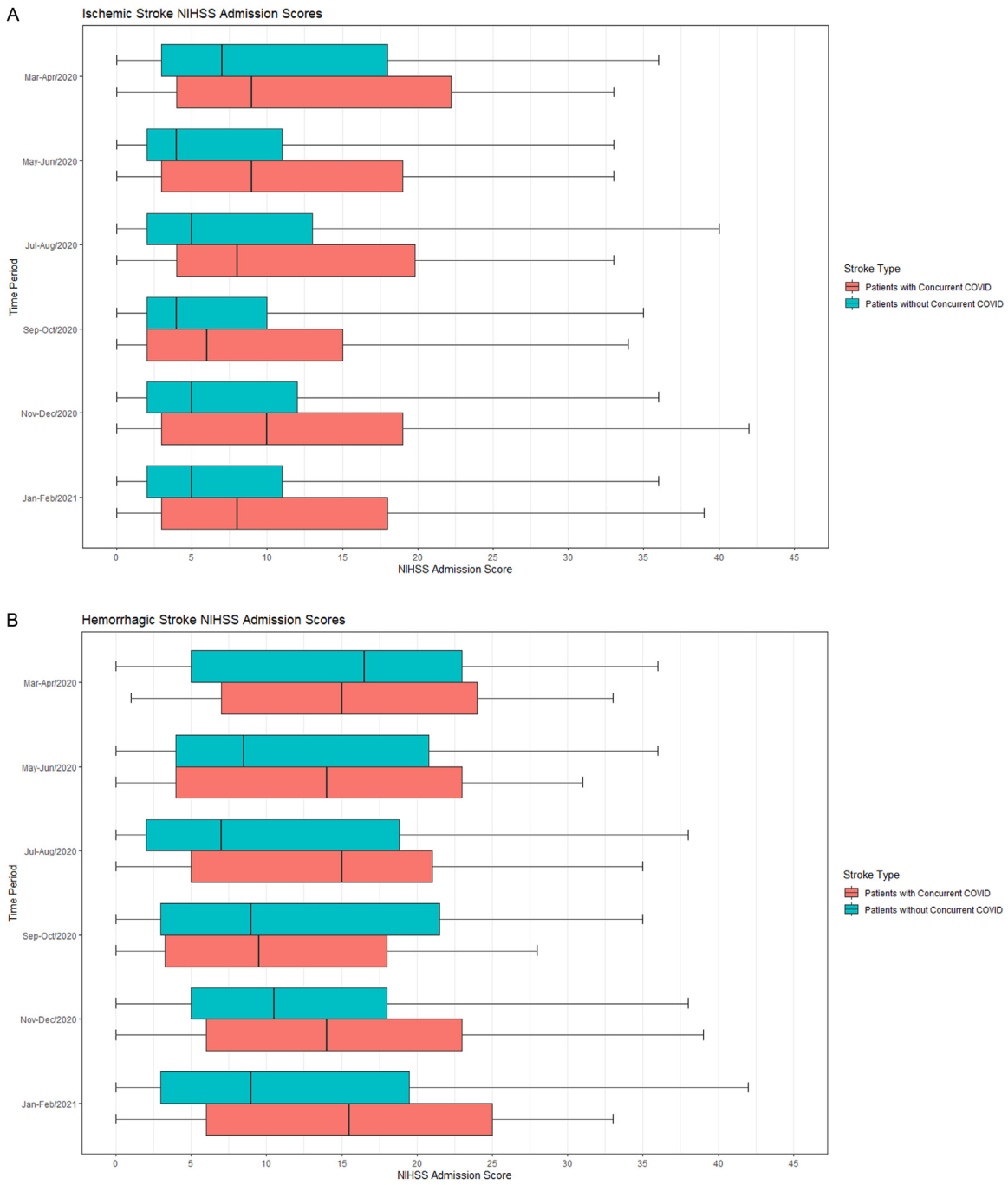

Fig. 3. *A box plot of stroke severity (NIHSS) in Propensity Score Matched Samples by 2-Month Epoch.*

their positive SARS-COV-2 test. This is to be expected given the fact that testing for SARS-COV-2 infection has become largely routine at the time of admission to hospitals. However, what is interesting is the higher-than-normal rates of stroke in the weeks following the first positive SARS-COV-2 test. We see a logarithmic decline in stroke rates as we move away from the lab-positive index date, with rates normalizing at low levels about 40 days after a positive SARS-COV-2 test. There are no additional peaks observed. These data reveal a temporal relationship between SARS-COV-2 infection and stroke, suggesting that time of SARS-COV-2 infection is potential a risk factor for IS or HS.

This study has several limitations. First, we were unable to control for severity of COVID-19 illness. Admission to an ICU, IMV and ECMO may be reasonable biomarkers or surrogates of SARS-CoV-2 infection severity. However, patients suffering severe stroke may require admission to an ICU with need of IMV or ECMO as well, so we avoided using these as proxy indicators for SARS-CoV-2

Table 2. *Model results of ischemic and hemorrhagic stroke outcomes between patients with and without concurrent SARS-CoV-2 infection after propensity score matching.*

	Propensity score matched model outcomes					
	Ischemic Stroke			Hemorrhagic Stroke		
Outcome	Estimand	Parameter	*p*-value	Estimand	Parameter	*p*-value
NIHSS	IRR	1.43 (1.33, 1.52)	< 0.001	IRR	1.20 (1.08, 1.33)	< 0.001
Death	OR	2.19 (1.79, 2.69)	< 0.001	OR	2.05 (1.47, 2.87)	< 0.001
Log LOS	–	1.49 (1.37, 1.61)	< 0.001	–	1.25 (1.06, 1.47)	0.007
Time to Death	HR	1.51 (1.21, 1.89)	< 0.001	HR	1.31 (0.94, 1.47)	0.110

The acute stroke with non-concurrent SARS-CoV-2 infection is the reference group for all modeled outcomes. Log LOS (length of stay in days) should be interpreted as the length of stay of acute stroke diagnoses with concurrent SARS-CoV-2 infection is "parameter" times as long as those with non-concurrent SARS-CoV-2 infection. IRR = Incidence rate ratio, OR = Odds Ratio, HR = Hazards ratio.

infection severity. It is reasonable to expect that patients who are critically ill with COVID-19 and have a stroke might have a greater NIHSS due to difficulties interacting with the exam related to encephalopathy, intubation, or sedation that may accompany severe COVID-19 syndromes. Another limitation of our dataset is that only a small proportion of our entire sample had documented NIHSS on admission. There is concern that reporting bias might have affected results with NIHSS data missing more so in patients with COVID-19 than without (IS 84.7% vs 71.9% and HS 82.3% vs 87.6%). Although, we performed exact matching on enrollment site to control for differences in reporting practices that might vary across sites. Additionally, this study is limited by the retrospective design and the nature of EHR data that construct the N3C. Thus, our estimates of mortality may be affected by loss to follow up. Finally, while these data add to the literature by contributing an analysis spanning the first year of the pandemic, our results are not necessarily generalizable to subsequent COVID-19 variants and waves of the pandemic. This fact necessitates further research of other COVID-19 variants. Further work is also needed to define the treatment effects on outcomes in patients with stroke and concurrent SARS-COV-2 infection, especially stroke subtypes.

In conclusion, in this large multicenter dataset from the first year of the pandemic, we found that stroke severity, mortality, and length of stay were increased in patients with both acute ischemic and hemorrhagic stroke hospitalizations with concurrent SARS-COV-2 infection. Additionally, we found a temporal association of concomitant stroke and SARS-CoV-2 infection with rates of stroke being elevated for approximately 40 days after initial positive test. Further research is needed to better understand the underlying causes of these associations and to confirm whether these trends continued during the subsequent course of the pandemic.

Grant Support and Disclosures

Jackson Narrett: None.

Indika Mallawaarachchi: None.

Chad Aldridge: None.

Ethan Assefa: None.

Arti Patel: None.

Johanna Loomba: None.

Sarah Ratcliffe: None.

Ofer Sadan: None.

Teshamae Monteith: Other; Modest; Impel, Amgen, Eli Lilly, Other; Significant; Amgen, AbbVie.

Bradford Worrall: Other; Significant; American Academy of Neurology, 2018 Fulbright Distinguished Chair in Health University of Newcastle and Hunter Medical Research Institute Harrison, Research Grant; Significant; NINDS Grant: R21 NS106480 (Gastrointestinal Microbiome and STroke Outcomes NEtwork (GeMSTONE) Grant PI);, NINDS Grant: U24 NS107222 (Stroke Central Atlantic Network for Research co-PI StrokeNet RCC), NCATS Grant: KL2TR003016 (integrated Translational Health Institute of Virginia (iTHRIV) CTSA. co-PI for KL-2 grant), NIA Grant: R01AG072592 Cerebral small vessel disease burden and racial disparity in vascular cognitive impairment and Alzheimer's disease and its related dementias. co-Investigator.

Donald Brown: None.

Karen Johnston: Honoraria; Modest; ANA,AAN, AUPN, FDA, NINDS, Other Research Support; Modest; Biogen, Research Grant; Modest; NIH-NHLBI, Rivanna Medical, Research Grant; Significant; NIH-NINDS, NIH-NCATS, Diffusion Pharm.

Andrew Southerland: Expert Witness; Modest; Medicolegal consultation, vascular neurology, Other; Modest; U.S. Patent No. 10,846,370, U.S. Provisional Patent Application No. 62/620,096 (BANDIT); Research Grant; Modest; Abbvie Pharmaceuticals, Inc., Research Grant; Significant; Diffusion Pharmaceuticals, Inc., American Heart Association/American Stroke Association.

Acknowledgments: N3C Attribution

The analyses described in this publication were conducted with data or tools accessed through the NCATS N3C Data Enclave covid.cd2h.org/enclave and supported by NCATS

U24 TR002306. This research was possible because of the patients whose information is included within the data from participating organizations (covid.cd2h.org/dtas) and the organizations and scientists (covid.cd2h.org/duas) who have contributed to the on-going development of this community resource (cite this https://doi.org/10.1093/jamia/ocaa196).

IRB

The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources.

Individual Acknowledgements For Core Contributors

We gratefully acknowledge contributions from the following N3C core teams: (Asterisks indicate leads) • Principal Investigators: Melissa A. Haendel*, Christopher G. Chute*, Kenneth R. Gersing, Anita Walden

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Additional Data Partners Who Have Signed a DTA and Whose Data Release is Pending

The Rockefeller University — UL1TR001866: Center for Clinical and Translational Science • The Scripps Research Institute — UL1TR002550: Scripps Research Translational Institute • University of Texas Health Science Center at San Antonio — UL1TR002645: Institute for Integration of Medicine and Science • The University of Texas Health Science Center at Houston — UL1TR003167: Center for Clinical and Translational Sciences (CCTS) • NorthShore University HealthSystem — UL1TR002389: The Institute for Translational Medicine (ITM) • Yale New Haven Hospital — UL1TR001863: Yale Center for Clinical Investigation • Emory University — UL1TR002378: Georgia Clinical and Translational Science Alliance • Weill Medical College of Cornell University — UL1TR002384: Weill Cornell Medicine Clinical and Translational Science Center • Montefiore Medical Center — UL1TR002556: Institute for Clinical and Translational Research at Einstein and Montefiore • Medical College of Wisconsin — UL1TR001436: Clinical and Translational Science Institute of Southeast Wisconsin • University of New Mexico Health Sciences Center — UL1TR001449: University of New Mexico Clinical and Translational Science Center • George Washington University — UL1TR001876: Clinical and Translational Science Institute at Children's National (CTSA-CN) • Stanford University — UL1TR003142: Spectrum: The Stanford Center for Clinical and Translational Research and Education • Regenstrief Institute — UL1TR002529: Indiana Clinical and Translational Science Institute • Cincinnati Children's Hospital Medical Center — UL1TR001425: Center for Clinical and Translational Science and Training • Boston University Medical Campus — UL1TR001430: Boston University Clinical and Translational Science Institute • The State University of New York at Buffalo — UL1TR001412: Clinical and Translational Science Institute • Aurora Health Care — UL1TR002373: Wisconsin Network For Health Research • Brown University — U54GM115677: Advance Clinical Translational Research (Advance-CTR) • Rutgers, The State University of New Jersey — UL1TR003017: New Jersey Alliance for Clinical and Translational Science • Loyola University Chicago — UL1TR002389: The Institute for Translational Medicine (ITM) • #N/A — UL1TR001445: Langone Health's Clinical and Translational Science Institute • Children's Hospital of Philadelphia — UL1TR001878: Institute for Translational Medicine and Therapeutics • University of Kansas Medical Center — UL1TR002366: Frontiers: University of Kansas Clinical and Translational Science Institute • Massachusetts General Brigham — UL1TR002541: Harvard Catalyst • Icahn School of Medicine at Mount Sinai — UL1TR001433: ConduITS Institute for Translational Sciences • Ochsner Medical Center — U54GM104940: Louisiana Clinical and Translational Science (LA CaTS) Center • HonorHealth — None (Voluntary) • University of California, Irvine — UL1TR001414: The UC Irvine Institute for Clinical and Translational Science (ICTS) • University of California, San Diego — UL1TR001442: Altman Clinical and Translational Research Institute • University of California, Davis — UL1TR001860: UCDavis Health Clinical and Translational Science Center • University of California, San Francisco — UL1TR001872: UCSF Clinical and Translational Science Institute • University of California, Los Angeles — UL1TR001881: UCLA Clinical Translational Science Institute • University of Vermont — U54GM115516: Northern New England Clinical & Translational Research (NNE-CTR)

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2023.106987.

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