Mortality following mechanical thrombectomy for ischemic stroke in patients with COVID-19

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Objectives: Multiple prior studies have shown a relationship between COVID-19 and strokes; further, COVID-19 has been shown to influence both time-to-thrombectomy and overall thrombectomy rates. Using large-scale, recently released national data, we assessed the association between COVID-19 diagnosis and patient outcomes following mechanical thrombectomy. Materials and methods: Patients in this study were identified from the 2020 National Inpatient Sample. All patients with arterial strokes undergoing mechanical thrombectomy were identified using ICD-10 coding criteria. Patients were further stratified by COVID diagnosis (positive vs. negative). Other covariates, including patient/hospital demographics, disease severity, and comorbidities were collected. Multivariable analysis was used to determine the independent effect of COVID-19 on in-hospital mortality and unfavorable discharge. Results: 5078 patients were identified in this study; 166 (3.3%) were COVID-19 positive. COVID-19 patients had a significantly higher mortality rate (30.1% vs. 12.4%, p < 0.001). When controlling for patient/hospital characteristics, APR-DRG disease severity, and Elixhauser Comorbidity Index, COVID-19 was an independent predictor of increased mortality (OR 1.13, p = 0.002). COVID-19 was not significantly related to discharge disposition (p = 0.480). Older age and increased APR-DRG disease severity were also correlated with increase morality. Conclusions: Overall, this study indicates that COVID-19 is a predictor of mortality among mechanical thrombectomy. This finding is likely multifactorial but may be related to multisystem inflammation, hypercoagulability, and re-occlusion seen in COVID-19 patients. Further research would be needed to clarify these relationships. Keywords: Stroke—Thrombectomy—Mortality—COVID-19—Coronavirus © 2023 Elsevier Inc. All rights reserved.

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Introduction

Cerebrovascular accident (CVA), or stroke, is an extremely common pathology in the United States, affecting nearly 800,000 patients per year. Treatment for stroke is highly variable and depends greatly on presenting factors and time to presentation; however, if indicated, mechanical thrombectomy is often the ideal treatment modality for large-vessel occlusions.

With the onset of the coronavirus-19 (COVID-19) global pandemic, millions of patients have been impacted by disruptions in healthcare.³ Due to its effect on hospital workflow, patient volume, and acuity of illness, COVID-19 has affected not only patients primarily hospitalized with COVID-19, but also patients with sequelae of systemic infections or patients coincidentally diagnosed with COVID-19.⁴⁻⁸ Furthermore, hospitals were required to reorganize ICU management and care processes to meet the increased demands of these patients.⁴⁻⁸ Despite these efforts, COVID-19 still led to significant delays and/or cancellations of many urgent, non-elective procedures, including stroke treatment.⁹⁻¹¹

Among many systemic sequelae of COVID-19, it has been shown to have a significant relationship with ischemic stroke. This is likely, at least in part, due to multisystem dysfunction, inflammation, and hypercoagulability. 12,13 Previous studies have reported up to a 9.4% incidence of ischemic stroke among COVID-19 patients, although reported incidences varied widely within the literature. 12,14 However, prior studies have reported that severe COVID-19 infection is associated with an increase in ischemic stroke risk as well as increased stroke severity. 12,14

With the onset of the COVID-19 pandemic, various facilities have also documented decreased rates of mechanical thrombectomy for stroke patients, and COVID-19 surges were found to be associated with increased time to mechanical thrombectomy. ^{15,16} These delays in stroke treatment may play a role in adverse patient outcomes, but prior studies have only examined small patient cohorts, limiting their generalizability. Specifically, the outcomes of mechanical thrombectomy patients with and without COVID-19 have yet to be examined with a large national dataset.

In this study, the National Inpatient Sample (NIS) database from April 2020 to December 2020 was utilized to evaluate demographics, mortality rates, and unfavorable discharge for mechanical thrombectomy patients with and without COVID-19. Our hypothesis is that concurrent COVID-19 diagnosis in mechanical thrombectomy patients is associated with increased likelihood of mortality compared to mechanical thrombectomy patients without COVID-19.

Methods

Patient identification

Patients in this study were identified from the 2020 version of the National Inpatient Sample (NIS). The NIS is a

large administrative databased published as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ). The NIS is a discharge-level database the contains sociodemographic, diagnostic, and outcomes data from over 7 million United States hospitalizations per year. When weighted, this accounts for approximately 35 million annual hospitalizations. COVID-19 diagnosis was of particular interest to the investigators; as such, the 2020 year of the NIS (the most recently published edition) was chosen due to the addition of a specific ICD-10 code for proven COVID-19 diagnosis (U07.1); specifically, patients were taken from April to December of 2020 (COVID-19 coding was not available prior to April 2020).

The primary inclusion criteria selected for patients with arterial cerebral infarctions (I63.0X–163.5X, I63.81) that underwent mechanical thrombectomy (03CGXXX – 03CQXXX). Patients with cerebral infarction due to venous thrombosis and other/unspecified infarctions were excluded. Pediatric patients (less than 18 years old) or missing mortality/length of stay (LOS) data were also excluded. A flowchart detailing patient selection is provided in Fig. 1. A full list of ICD-10 codes used for patient inclusion/exclusion is provided in the supplementary material (Table S1).

Data collection

Additional patient-related information was obtained via multiple methods. Basic sociodemographic information was obtained directly from the NIS; this included age, sex, race, residence, income quartile, and insurance status. Hospital information was also collected (hospital bedsize, ownership structure, and US census division/region). Comorbidities were estimated by both (1) APR-DRG risk of mortality (obtained directly from the NIS) and (2) the Elixhauser Comorbidity Index (ECI; calculated from ICD-10 codes).

The primary outcomes in this study include (1) in-hospital mortality and (2) discharge disposition (which is a binary variable considered to be either "favorable" or "unfavorable"). For the purposes of this study, "unfavorable discharge" was defined as either (1) in-hospital mortality or (2) transfer to non-short-term care, such as skilled nursing facilities or intermediate care.

Statistical analysis

Patient demographics and clinical characteristics were reported by frequency/percentage for the entire cohort and further stratified by COVID-19 status. Differences between groups were evaluated using $\chi 2$ tests. Two types of multivariable regressions were used for assessing association between COVID-19 infection and outcomes: (1) Logistic regression for mortality, with results reported as odds ratios (OR), and (2) Log-binomial regression for discharge disposition, with results reported as relative

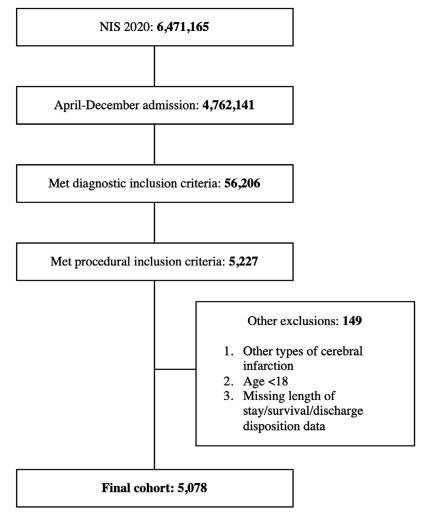


Fig. 1. Flowchart detailing patient selection criteria.

risks (RR). Both models used generalized estimation equations to incorporate hospital clustering. Hosmer-Lemeshow goodness-of-fit test was used to check logistic model assumptions. All covariates mentioned above were included in the model for adjustment. Missing data affected less than 4% of patients, so only admissions with no missing information regarding exposures, outcomes, or covariates were used for regression models. A p-value < 0.05 was considered statistically significant. Analysis was performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Patient demographics

The overall demographics of the patient cohort are summarized in Table 1. 5078 patients in the NIS underwent mechanical thrombectomy stroke from April to December 2020. Of those patients, 4912 were COVID-19 negative (96.7%), and 166 were COVID-19 positive (3.3%). When stratified by COVID-19 status, there were a number of differences noted for multiple demographic factors.

Patients with COVID-19 were more likely to be younger (37.3% 18-59 years of age for COVID-19 positive patients, 23.4% for COVID-19 negative patients, p < 0.001). Multiple demographic differences were noted among the two populations regarding both race and insurance status. As expected, patients with COVID-19 had worse risk of mortality and illness severity (per APR-DRG); however, there was no difference in the ECI.

Patients with COVID-19 were noted to have a higher mortality rate (30.1% vs. 12.4%, p < 0.001). Additionally, patients with COVID-19 were more likely to have unfavorable discharge disposition (74.1% vs. 63.9%, p = 0.007).

Patient outcomes

Predictors of in-hospital mortality among patients undergoing thrombectomy are shown in Table 2. Most notably, even when controlling for factors such as ECI and APR-DRG disease severity, concurrent COVID-19 diagnosis was an independent predictor of mortality (OR 1.13, p = 0.002). This means that, after adjusting for all other covariates, COVID-19 led to an independent

 Table 1. Demographic characteristics of all stroke thrombectomy patients stratified by COVID-19 status.

	T . 10 1 .	COMP	COMP (1)	1
	Total Cohort	COVID (-)	COVID (+)	p-value
Patient Count	5078	4912 (96.7%)	166 (3.3%)	
Age (years)				< 0.0001
18-44	314 (6.2%)	298 (6.1%)	16 (9.6%)	
45-59	897 (17.7%)	851 (17.3%)	46 (27.7%)	
60-74	1876 (37.0%)	1814 (36.9%)	62 (37.4%)	
75+	1991 (39.2%)	1949 (39.7%)	42 (25.3%)	
Sex				0.21
Male	2480 (48.8%)	2391 (48.7%)	89 (53.6%)	
Female	2598 (51.2%)	2521 (51.3%)	77 (46.4%)	
Race				< 0.0001
White	3294 (64.9%)	3223 (65.6%)	71 (42.8%)	
Black	773 (15.2%)	735 (15.0%)	38 (22.9%)	
Hispanic	426 (8.4%)	393 (8.0%)	33 (19.9%)	
Asian or Pacific Islander	170 (3.4%)	166 (3.4%)	DS*	
Native American	13 (0.3%)	11 (0.2%)	DS*	
Other	171 (3.4%)	160 (3.3%)	11 (6.6%)	
Missing	231 (4.6%)	224 (4.6%)	DS*	
Insurance				0.02
Medicare	3087 (60.8%)	3007 (61.2%)	80 (48.2%)	
Medicaid	557 (11.0%)	529 (10.8%)	28 (16.9%)	
Private Insurance	1093 (21.5%)	1052 (21.4%)	41 (24.7%)	
Self-Pay	177 (3.5%)	169 (3.4%)	DS*	
No Charge	16 (0.3%)	16 (0.3%)	0(0.0%)	
Other	137 (2.7%)	130 (2.7%)	DS*	
Missing	11 (0.2%)	DS*	DS*	
NCHS Urban/Rural Code				0.61
Central counties of metro areas of ≥ 1 million population	1560 (30.7%)	1500 (30.5%)	60 (36.1%)	
"Fringe" countries of metro areas of ≥ 1 million population	1238 (24.4%)	1199 (24.4%)	39 (23.5%)	
Counties in metro areas of 250,000-999,999 population	1075 (21.2%)	1042 (21.2%)	33 (19.9%)	
Counties in metro areas of 50,000-249,999 population	431 (8.5%)	417 (8.5%)	14 (8.4%)	
Micropolitan counties	410 (8.1%)	398 (8.1%)	12 (7.2%)	
Not metropolitan or micropolitan counties	341 (6.7%)	334 (6.8%)	DS*	
Missing	23 (0.5%)	22 (0.5%)	DS*	
Median Household Income (percentile)				0.17
0-25%	1443 (28.4%)	1387 (28.2%)	56 (33.7%)	
26-50%	1354 (26.7%)	1305 (26.6%)	49 (29.5%)	
51-75%	1181 (23.3%)	1148 (23.4%)	33 (19.9%)	
76-100%	1037 (20.4%)	1011 (20.6%)	26 (15.7%)	
Missing	63 (1.2%)	61 (1.2%)	DS*	
Hospital Bedsize				0.02
Small	367 (7.2%)	363 (7.4%)	DS*	
Medium	1094 (21.5%)	1050 (21.4%)	44 (26.5%)	
Large	3617 (71.2%)	3499 (71.2%)	118 (71.1%)	
Hospital Ownership				0.75
Government, nonfederal	606 (11.9%)	584 (11.9%)	22 (13.3%)	
Private, not-profit	3844 (75.7%)	3718 (75.7%)	126 (75.9%)	
Private, invest-own	628 (12.4%)	610 (12.4%)	18 (10.8%)	
Hospital Division				0.14
New England	190 (3.7%)	187 (3.8%)	DS*	
Middle Atlantic	701 (13.8%)	672 (13.7%)	29 (17.5%)	
East North Central	748 (14.7%)	719 (14.6%)	29 (17.5%)	
West North Central	368 (7.3%)	352 (7.2%)	16 (9.6%)	
South Atlantic	1126 (22.2%)	1094 (22.3%)	32 (19.3%)	
East South Central	384 (7.6%)	370 (7.5%)	14 (8.4%)	
West South Central	485 (9.6%)	465 (9.5%)	20 (12.1%)	
Mountain	355 (7.0%)	346 (7.0%)	DS*	
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Table 1 (*Continued*)

	Total Cohort	COVID (-)	COVID (+)	p-value
Pacific	721 (14.2%)	707 (14.4%)	14 (8.4%)	
Hospital Region				0.08
Northeast	891 (17.6%)	859 (17.5%)	32 (19.3%)	
Midwest	1116 (22.0%)	1071 (21.8%)	45 (27.1%)	
South	1995 (39.3%)	1929 (39.3%)	66 (39.8%)	
West	1076 (21.2%)	1053 (21.4%)	23 (13.9%)	
APR-DRG Risk of Mortality				< 0.0001
Minor	608 (12.0%)	607 (12.4%)	DS*	
Moderate	843 (16.6%)	838 (17.1%)	DS*	
Major	1027 (20.2%)	1006 (20.5%)	21 (12.7%)	
Extreme	2600 (51.2%)	2461 (50.1%)	139 (83.7%)	
APR-DRG Illness Severity	, ,	, ,	, ,	< 0.0001
Minor	49 (1.0%)	49 (1.0%)	0 (0%)	
Moderate	1117 (22.0%)	1116 (22.7%)	DS*	
Major	1508 (29.7%)	1481 (30.2%)	27 (16.3%)	
Extreme	2404 (47.3%)	2266 (46.1%)	138 (83.1%)	
Elixhauser Comorbidity Index	, ,	, ,	, ,	0.62
0	49 (1.0%)	49 (1.0%)	0 (0.0%)	
1	189 (3.7%)	183 (3.7%)	DS*	
2	578 (11.4%)	560 (11.4%)	18 (10.8%)	
≥3	4262 (83.9%)	4120 (83.9%)	142 (85.5%)	
Mortality	, ,	, ,	, ,	< 0.0001
No	4420 (87.0%)	4304 (87.6%)	116 (69.9%)	
Yes	658 (13.0%)	608 (12.4%)	50 (30.1%)	
Discharge Disposition	. ,	,	,	0.007
Unfavorable	3260 (64.2%)	3137 (63.9%)	123 (74.1%)	
Favorable	1818 (35.8%)	1775 (36.1%)	43 (25.9%)	

DS*: data suppressed - per NIS policy, specific patient counts are not provided for cells with less than 10 patients to protect patient anonymity

increase in mortality by 10%. Various demographic factors were related to mortality; not unsurprisingly, there is a direct relationship between age and morality rate. None of the assessed hospital factors (bedsize, census division, or ownership) were related to mortality rates. As expected, APR-DRG disease severity was directly correlated with mortality.

Similarly, predictors of unfavorable discharge disposition are shown in Table 3. Unlike mortality, COVID-19 diagnosis was found to have no significant relationship with discharge disposition (p = 0.480). Like mortality, advanced age was found to have a direct relationship with unfavorable discharge. Patient were less likely to have unfavorable discharge if they had private insurance (RR 0.93, p = 0.004) or were self-pay (RR 0.66, p < 0.001). APG-DRG disease severity was again found to be directly correlated with unfavorable discharge.

Discussion

As hypothesized, COVID-19 infection was associated with a higher likelihood of mortality among stroke patients that received thrombectomy, even when controlling for disease severity/comorbidities. Our analysis also showed an association between post-thrombectomy

mortality and (1) APR-DRG disease severity and (2) advanced age. To the best of our knowledge, this study is the first to leverage a large national dataset to compare mortality rates in stroke patients with and without COVID-19 who underwent mechanical thrombectomy.

Prior studies have demonstrated poor outcomes and high mortality rates among COVID-19 positive stroke patients despite appropriate treatment with thrombectomy. 11,17-19 One 2020 single-center analysis found that COVID-19 was an independent predictor for in-hospital mortality in stroke patients that received mechanical thrombectomy (OR 6.67, 95% Cl 1.1-40.4). A retrospective study of COVID-19 positive stroke patients that received mechanical thrombectomy found high complication rates, extensive clot burden, procedures requiring multiple attempts, and a high mortality rate. 13 Our study builds upon these findings by offering the perspective of a large-scale national database that can overcome many of the biases of small single-institution analyses.

In this study, we found that COVID-19 patients undergoing thrombectomy for treatment of stroke had a significantly increased likelihood of inpatient mortality than non-COVID patients (OR 1.13, 95% Cl 1.05-1.21). It's widely believed that COVID-19 may contribute to a high inflammatory state and hypoxemia, leading to cytokine-

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Table 2. Significant predictors of mortality among patient going mechanical thrombectomy.

going mechanic	going mechanical infombectomy.				
	OR (95% Cl)	p-value*			
Age					
<45	Ref				
45-59	1.02 (0.98-1.05)	0.343			
60-74	1.05 (1.01-1.09)	0.010			
≥75	1.08 (1.04-1.12)	< 0.001			
Race					
White	Ref				
Black	0.95 (0.93-0.98)	< 0.001			
Hispanic	1.03 (0.99-1.07)	0.158			
Asian or Pacific Islander	0.96 (0.91-1.00)	0.066			
Native American	0.88 (0.82-0.95)	0.001			
Other	0.99 (0.94-1.03)	0.548			
Primary Insurance					
Medicaid	Ref				
Medicare	1.02 (0.99-1.06)	0.189			
Private insurance	1.00 (0.97-1.03)	0.939			
Self-pay	1.06 (1.00-1.12)	0.039			
No charge	1.00 (0.87-1.16)	0.987			
Other	1.05 (0.99-1.12)	0.121			
Median household income ((percentile)				
0-25	Ref				
26-50	0.99 (0.96-1.01)	0.366			
51-75	0.98 (0.96-1.01)	0.290			
76-100	0.96 (0.93-0.99)	0.016			
APR-DRG Disease Severity	7				
Minor	Ref				
Moderate	1.01 (0.99-1.02)	0.271			
Major	1.04 (1.02-1.06)	< 0.001			
Extreme	1.24 (1.21-1.26)	< 0.001			
Elixhauser Comorbidity Sc	Elixhauser Comorbidity Score				
0	Ref				
1	0.88 (0.76-1.03)	0.103			
2	0.88 (0.75-1.02)	0.082			
<u>≥</u> 3	0.86 (0.74-1.00)	0.048			
COVID					
No	Ref				
Yes	1.13 (1.05-1.21)	0.002			

^{*}Significance calculated via multivariable logistic regression

storm-triggered coagulopathies. 21-24 Many studies have reported high re-occlusion rates among COVID-19 patients treated with thrombectomy, potentially related to a hypercoagulable state induced by infection. 25 Microvascular inflammation and endotheliitis could also contribute to higher rates of complications and re-occlusions in COVID patients receiving thrombectomy. 19,26,27 Still, other explanations should also be explored; patients with underlying cardiovascular disease and risk factors are more likely to develop severe cases of COVID-19 and may also contribute to a higher probability of serious complications and poor outcomes from stroke. 28,29 Further investigation into the pathophysiology underlying COVID-related stroke and complications leading to poor

outcomes in COVID patients post-thrombectomy is necessary.

Interestingly, while COVID-19 was shown to have a significant effect on in-hospital mortality, it did not appear to effect overall disposition (i.e. favorable vs. unfavorable). While mortality is included in the definition "unfavorable discharge", it also includes discharge to skilled nursing facilities and intermediate care (whereas "favorable discharge" includes routine home discharges, short-term care, and home health). As such, while mortality is more inherently related to both stroke severity and systemic disease burden, discharge disposition is also tied to a patient's functional status following a stroke. While the effect of COVID-19 on systemic disease burden and subsequent mortality is more straightforward, it may be that COVID-19 has little to no independent effect on a patient's functional status following a stroke.

Our study also found that several demographics significantly impacted likelihood of mortality post-thrombectomy. Patients that self-paid (did not have/use health insurance) had a higher likelihood of mortality postthrombectomy compared to Medicare patients, while patients in the 76-100th percentile of median household income had a lower likelihood of mortality post-thrombectomy. Similar trends in disparities across insurance and income have been observed in other studies; one analysis of NIS data from 2006-2016 found that 4th quartile median household income (OR 1.10, 95% Cl 1.06-1.14) and private insurance (OR 1.36, 95% Cl 1.31-1.39) were predictors of good outcome following mechanical thrombectomy. 30,31 These trends may be confounded by decreased access to preventative care among patients with lower income or poor insurance coverage, contributing to both the severity of stroke and response to treatment. There may also be variation in time to presentation to medical care and access to quality treatments and hospitals. Further review of these factors and others would be needed to investigate this.

Limitations

As with all NIS-based studies, this project has a set of limitations that are present in nearly all studies with data from administrative databases. Given that diagnoses are characterized by ICD-10 codes, only diagnostic data with a corresponding ICD-10 code can be utilized. Additionally, any administrative database is subject to a certain rate of coding inaccuracies, and this is impossibly to retrospectively verify. While administrative databases are useful in their ability to assess large amounts of patients, they cannot imply direct causality. Lastly, the NIS is a discharge-level database and not a patient-level database; as such, patients are not trackable across multiple hospital stays, thereby limiting assessment of long-term outcomes (such as post-discharge mortality).

Table 3. Significant predictors of unfavorable discharge among patient going mechanical thrombectomy.

	RR (95% Cl)	p-value*
Age		
<45	Ref	
45-59	1.14 (1.02-1.26)	0.018
60-74	1.24 (1.11-1.38)	< 0.001
≥75	1.23 (1.11-1.37)	< 0.001
Race		
White	Ref	
Black	0.97 (0.93-1.02)	0.244
Hispanic	0.97 (0.90-1.04)	0.354
Asian or Pacific Islander	0.75 (0.64-0.87)	< 0.001
Native American	0.85 (0.59-1.23)	0.389
Other	0.92 (0.82-1.03)	0.138
Primary Insurance		
Medicare	Ref	
Medicaid	0.97 (0.91-1.04)	0.458
Private insurance	0.93 (0.88-0.98)	0.004
Self-pay	0.66 (0.56-0.78)	< 0.001
No charge	0.44 (0.17-1.19)	0.105
Other	0.82 (0.71-0.94)	0.004
Census Division of Hospital		
New England	Ref	
Middle Atlantic	0.99 (0.92-1.06)	0.775
East North Central	1.02 (0.96-1.09)	0.535
West North Central	0.93 (0.85-1.01)	0.077
South Atlantic	0.98 (0.92-1.05)	0.585
East South Central	0.98 (0.90-1.07)	0.648
West South Central	0.97 (0.89-1.04)	0.387
Mountain	1.00 (0.94-1.08)	0.903
Pacific	0.82 (0.74-0.90)	< 0.001
APR-DRG Disease Severity		
Minor	Ref	
Moderate	2.17 (1.12-4.18)	0.021
Major	3.15 (1.63-6.08)	< 0.001
Extreme	4.26 (2.20-8.23)	< 0.001
Elixhauser Comorbidity Sco	ore	
0	Ref	
1	0.75 (0.62-0.92)	0.006
2	0.87 (0.75-1.01)	0.074
<u>≥</u> 3	0.93 (0.80-1.07)	0.279
COVID		
No	Ref	
Yes	0.97 (0.89-1.06)	0.480

^{*}Significance calculated via multivariable log-binomial regression

Also of note, as the NIS is a large and generalized database for all tyles of hospital admissions; while this proves beneficial in obtaining large patient samples, it does not include stroke-specific information that is not readily codable via ICD-10 codes. For example, information on stroke severity (such as the NIH Stroke Scale) and the amount of time from stroke onset until presentation are not available and likely act as confounders in the data. Similarly, specifics of individual thrombectomies (such door-to-puncture time or procedural difficulty) are unable to be assessed.

Conclusions

In this study, the relationship between COVID-19, stroke, and outcomes following mechanical thrombectomy are assessed using a large, administrative database (the NIS). Specifically, it was hypothesized that patients with COVID-19-related strokes would have higher mortality rates following mechanical thrombectomy, even when controlling for disease severity and comorbidities. After a review of all patients in the NIS undergoing thrombectomy from April to December of 2020, COVID-19 was found to be an independent predictor of increased mortality rates. Although the exact causal relationship cannot be established, it is likely multifactorial and may be related to multisystem inflammation, hypercoagulability, and re-occlusion seen in COVID-19 patients. Further research would be needed to identify the pathophysiological relationship of this finding.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecere brovasdis.2023.107171.

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