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

The Effect of COVID-19 Vaccines on Stroke Outcomes: A Single-Center Study

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BACKGROUND: **One of the defining narratives of the COVID-19 pandemic has been the acceptance and distribution of vaccine. To compare the outcomes of COVID-19 positive vaccinated and unvaccinated stroke patients.**

METHODS: **This is a single-center retrospective study of COVID-19-vaccinated and unvaccinated stroke patients between April 2020 and March 2022. All patients presenting with stroke regardless of treatment modalities were included. National Institutes of Health Stroke Scale was used to assess stroke severity. The primary outcome was functional capacity of the patients at discharge.**

RESULTS: **The study cohort comprised 203 COVID-19 positive stroke patients divided into 139 unvaccinated and 64 fully vaccinated patients. At discharge, the modified Rankin scale score was significantly lower in the vaccinated cohort (3[1–4] vs. 4[2–5], odds ratio = 0.508, P = 0.011). At 3 months of follow-up, the median modified Rankin scale score was comparable between both cohorts.**

CONCLUSIONS: **Although vaccination did not show any significant difference in stroke patient outcomes on follow-up, vaccines were associated with lower rates of morbidity and mortality at discharge among stroke patients during the pandemic.**

INTRODUCTION

After COVID-19 was declared a public health emergency by the World Health Organization, it was not until 9 months later that the first American outside of a clinical trial received the first dose of the vaccine.[1,2] In our prior study and associated literature it has been established that COVID-19 is an independent factor of unfavorable outcomes in stroke patients.[3,4] Despite finding an association between COVID-19 and stroke severity, information on how COVID-19 vaccination could have any further impact on patients with strokes remains scarce. In this study we compare the outcomes of vaccinated and unvaccinated COVID-19 positive-stroke patients to provide further evidence about the efficacy of vaccines in decreasing stroke severity and improving stroke outcomes.

MATERIALS AND METHODS

Patient Population

This was a single-center retrospective study of COVID-19-positive vaccinated and unvaccinated stroke patients between April 2020 and March 2022. The institutional review board of participating institutions reviewed and approved the study, and patient consent was waived.

Diagnosis of COVID-19 was established using reverse-transcriptase–polymerase-chain-reaction assays of nasopharyngeal samples for identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 vaccines included the following: 1) Comirnaty (BNT 162b2 mRNA vaccine) by Pfizer

Key words
- COVID-19
- Stroke
- Vaccination

Abbreviations and Acronyms
ANCOVA: Analysis of Covariance
ASPECTS: Alberta Stroke Program Early Computed Tomography Score
COVID-19: Coronavirus Disease 2019
LVO: Large Vessel Occlusion
mRS: modified Rankin Scale
NIHSS: National Institute of Health Stroke scale
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
tPA: tissue plasminogen activator

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Citation: World Neurosurg. (2023) 170:e834-e839. https://doi.org/10.1016/j.wneu.2022.11.132

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

BionTech, 2) Ad26.COV2. S adenovirus vaccine by Johnson & Johnson/Janssen, and 3) Spikevax (mRNA-1273vaccine) by Moderna. The inclusion criteria was all COVID-19-positive patients presenting with stroke regardless of treatment modalities during the study timeline.

Charts were reviewed and collected data for the pandemic cohort included the following: 1) baseline characteristics including age, gender, and race; 2) past medical and social history; 3) Vaccination status including unvaccinated, and fully vaccinated defined as at least 2 doses of vaccination (2 doses, 3 doses, or 4 doses) (Moderna or Pfizer) or 1 dose for Janssen; 4) stroke characteristics included the Alberta stroke program early computed tomography score, National Institutes of Health Stroke Scale score (NIHSS), and number of tandem occlusions; 5) treatment characteristics included tissue plasminogen activator administration and the need for mechanical thrombectomy; and 6) Functional outcomes included modified Rankin scale (mRS) at discharge, and at 3 months of follow-up and mortality. For the prepandemic cohort, the NIHSS score on admission was collected.

Primary and Secondary Outcomes

The primary outcome was the functional capacity of the patients at discharge based on ordinal mRS shift analysis. Secondary outcomes included NIHSS at 24 hours postprocedure, NIHSS at discharge, mortality at discharge, mRS up to 3 months of follow-up, mortality up to 3 months, NIHSS up to 3 months, the need for decompressive hemicraniectomy, and the length of hospital stay. Good functional outcome was defined by mRS 0–2, and poor functional outcome was defined by mRS 3–6.

Statistical Analysis

All statistical analyses were performed using the Stata software (version 17.0, College Station, Texas, USA). The remaining methods section is in the supplementary material folder. Following the pandemic, the cohort was divided into unvaccinated and vaccinated groups. Between-group baseline characteristics were compared using $\chi 2$ or Fisher's exact tests for categorical variables, and Student's t or Mann-Whitney U tests for continuous variables, where appropriate. Associations between outcomes and vaccination groups were assessed using ordinal logistic, binary logistic, and linear regression, wherever appropriate. Odds ratios (ORs) or betas and corresponding 95% confidence intervals were reported. Fisher's exact test was performed for outcomes with zero frequency cells. These relationships were then adjusted in multivariable models including baseline variables with P values < 0.100 in univariable comparisons. All tests were two-tailed, and P value of < 0.050 was considered statistically significant. Missing data were not imputed.

RESULTS

The study cohort consisted of 203 COVID-19 positive stroke patients divided into 139 unvaccinated patients and 64 fully vaccinated patients.

Comparison of Baseline Characteristics Between Fully Vaccinated and Unvaccinated COVID-19 Positive Patients Presenting with Stroke

With respect to patient demographics, the mean age, gender, and race distributions were comparable between both cohorts. With respect to past medical history, the number of patients with atrial fibrillation (34.4% vs.19.4%; P = 0.021), and peripheral vascular disease (17.2% vs.7.2%; P = 0.03) was significantly higher in the vaccinated cohort compared to the unvaccinated cohort. On admission, the number of patients on antiplatelet and anticoagulation medications was comparable between both cohorts. Compared to fully vaccinated patients, unvaccinated patients had a significantly higher admission NIHSS (median:10[3–19] vs. 4 [1.5–9]; P < 0.001). Lastly, the number of patients requiring mechanical thrombectomy was significantly higher in the unvaccinated cohort (27.3% vs.12.5%; P = 0.019) (**Table 1**).

Comparison of Outcomes Between Fully Vaccinated and Unvaccinated COVID-19 Positive Patients Presenting with Strokes

At discharge, the mRS score was significantly lower in the vaccinated cohort compared to the unvaccinated cohort (3[1–4] vs. 4 [2–5], OR = 0.508[0.301–0.859]; P = 0.011) before adjustment but was not significant after adjustment (OR = 0.490[0.211–1.139]; P = 0.098). This was further dissected in the secondary outcomes which showed a significantly higher rate of mRS (0–1) at discharge in the vaccinated cohort (37.5% vs. 23.9%, OR = 1.913 [1.005–3.639]; P = 0.048), which did not remain significant after adjustment (OR = 1.733[0.583–5.149]; P = 0.322), and a significantly higher rate of mRS (0–2) in the vaccinated cohort before adjustment (45.3% vs. 30.6% OR = 1.879[1.017–3.473]; P = 0.044) but not after adjustment (OR = 2.278[0.757–6.858]; P = 0.143). Also, median NIHSS score was significantly higher in the unvaccinated cohort compared to the vaccinated cohort at 24 hours (6 [1–19] vs. 3[1–8]; P = 0.008) and at discharge (6 [1–21] vs. 2[0–6]; P = 0.003) before adjustment, but did not remain significant after adjustment (P = 0.122) (P = 0.149), respectively. Interestingly, the mortality rate at discharge was significantly higher in the unvaccinated cohort (20.2% vs. 7.8%, OR = 0.336[0.123–0.918]; P = 0.033) before adjustment but did not remain significant after adjustment (OR = 0.556(0.069–4.479); P = 0.581). At 3 months of follow-up, the median mRS, median NIHSS, and mortality rates were comparable between both cohorts. Though not significant, the rate of decompressive hemicraniectomy was 4-times higher in the unvaccinated cohort (4.4% vs. 0.9%; P = 0.180). Lastly, the median length of stay was comparable between both cohorts (6 [3–14] vs. 5[3–10]; P = 0.009) before adjustment; however, this did not remain significant after adjustment (P = 0.059) (**Table 2**).

DISCUSSION

Vaccines against SARS-CoV-2 have been approved and used worldwide with unprecedented speed and it has been established that these vaccines provided critical protection against SARS-CoV-2.[5-7] While most studies assessed the overall efficacy and safety vaccination, reports on the effect of vaccination on stroke severity specifically remain scarce.[7-10] This study demonstrated that in general, the severity of strokes and large vessel occlusions (LVOs) has significantly increased after the pandemic in both COVID-19

Table 1. Comparison of Baseline Characteristics Between COVID-19-Positive Unvaccinated Versus Fully Vaccinated Patients Presenting with Stroke

	Unvaccinated (n = 139)	Fully Vaccinated (n = 64)	*P*-Value
Age, mean (SD) years	65.8 (15.2)	67.7 (13.9)	0.391
Male, n (%)	75/139 (54.0)	33/64 (51.6)	0.751
Race, n (%)			0.805
Caucasian	80/138 (58.0)	40/64 (62.5)	
African America	41/138 (29.7)	17/64 (26.6)	
Asian	11/138 (8.0)	3/64 (4.7)	
Hispanic	5/138 (3.6)	3/64 (4.7)	
Other	1/138 (0.7)	1/64 (1.6)	
Hypertension, n (%)	104/139 (74.8)	55/64 (85.9)	0.074
Diabetes mellitus, n (%)	60/139 (43.2)	24/64 (37.5)	0.446
CHF, n (%)	15/139 (10.8)	10/64 (15.6)	0.330
Cancer, n (%)	16/139 (11.5)	9/64 (14.1)	0.607
Atrial fibrillation, n (%)	27/139 (19.4)	22/64 (34.4)	**0.021**
Prior stroke, n (%)	33/139 (23.7)	20/63 (31.8)	0.231
PVD, n (%)	10/139 (7.2)	11/64 (17.2)	**0.030**
Immunosuppression, n (%)	8/139 (5.8)	5/64 (7.8)	0.553
Chronic lung disease, n (%)	21/139 (15.1)	8/64 (12.5)	0.622
Baseline mRS, median (IQR)	0 (0–1)	0 (0–2)	0.107
Antiplatelet use, n (%)	35/138 (25.4)	21/64 (32.8)	0.271
Anticoagulant use, n (%)	21/138 (15.2)	13/64 (20.3)	0.368
Smoking status, n (%)			0.827
None	93/137 (67.9)	42/64 (65.6)	
Current	21/137 (15.3)	12/64 (18.8)	
Former	23/137 (16.8)	10/64 (15.6)	
NIHSS, median (IQR)	10 (3–19)	4 (1.5–9)	**<0.001**
ASPECTS, median (IQR)	10 (9–10)	10 (10–10)	**0.022**
Tandem occlusion, n (%)	12/104 (11.5)	1/49 (2.0)	0.062
IV tPA, n (%)	28/136 (20.6)	10/61 (16.4)	0.490
Thrombectomy, (n%)	38/139 (27.3)	8/64 (12.5)	**0.019**

Bold values indicate stasticially significant.
SD, standard deviation; CHF, congestive heart failure; PVD, Peripheral vascular disease; mRS, modified Rankin scale; IQR, Interquartile range; NIHSS, National Institutes of Health Stroke Scale score; ASPECTS, Alberta stroke program early computed tomography score; IV, intravenous; tPA, tissue plasminogen activator.

positive and negative patients compared to the prepandemic. This corroborates what has been established in prior studies that COVID-19 is an independent predictor of poor functional outcome and mortality in stroke patients.[3,4,11,12] As for prognosis, compared to fully vaccinated patients, unvaccinated patients with strokes not only had significantly worse functional outcomes at discharge compared to vaccinated patients (mRS 4 [2–5] vs. 3 [1–4], OR = 0.508 [0.301–0.859]; P = 0.011 and NIHSS at discharge 6 [1–21] vs. 2 [0–6]; P = 0.003), but also mortality rate was 3 times higher than vaccinated patients (20.2% vs. 7.8%, OR = 0.336 [0.123–0.918], P = 0.033). Although functional outcome at 3 months of follow-up was comparable between cohorts, this may be due to several reasons. First, because mortality rate in the unvaccinated cohort was significantly higher compared to the vaccinated cohort, this means that fewer patients from the unvaccinated cohort with severe symptoms survived, which may have underestimated the rate of unfavorable outcomes at 3 months for the unvaccinated cohort. Another cause may be the

Table 2. Comparison of Outcomes Between COVID-19-Positive Unvaccinated Versus Fully Vaccinated Patients Presenting with Stroke

	Unvaccinated	Vaccinated	Effect Variable	Unadjusted Value (95% CI)	Unadjusted *P*-value	Adjusted Value (95% CI)*	Adjusted *P*-Value*
Primary Outcome							
mRS at discharge, median (IQR)	4 (2—5)	3 (1—4)	Common Odds Ratio	0.508 (0.301—0.859)	**0.011**	0.490 (0.211—1.139)	0.098
Secondary Outcomes							
mRS 0—1 at discharge, n (%)	32/134 (23.9)	24/64 (37.5)	Odds Ratio	1.913 (1.005—3.639)	**0.048**	1.733 (0.583—5.149)	0.322
mRS 0—2 at discharge, n (%)	41/134 (30.6)	29/64 (45.3)	Odds Ratio	1.879 (1.017—3.473)	**0.044**	2.278 (0.757—6.858)	0.143
NIHSS at 24 hours, median (IQR)	6 (1—19)	3 (1—8)	Beta	−4.062 (−7.072—−1.053)	**0.008**	−1.919 (−4.362—0.524)	0.122
NIHSS at discharge, median (IQR)	6 (1—21)	2 (0—6)	Beta	−6.882 (−11.363—−2.401)	**0.003**	−3.589 (−8.490—1.312)	0.149
Mortality at discharge, n (%)	27/134 (20.2)	5/64 (7.8)	Odds Ratio	0.336 (0.123—0.918)	**0.033**	0.556 (0.069—4.479)	0.581
mRS at 3 months, median (IQR)	6 (3—6)	6 (1—6)	Common Odds Ratio	0.872 (0.251—3.035)	0.830	0.882 (0.110—7.085)	0.906
mRS 0—1 at 3 months, n (%)	10/55 (18.2)	3/11 (27.3)	Odds Ratio	1.688 (0.379—7.513)	0.492	2.365 (0.167—33.495)	0.524
mRS 0—2 at 3 months, n (%)	12/55 (21.8)	4/11 (36.4)	Odds Ratio	2.048 (0.512—8.181)	0.311	3.177 (0.246—40.962)	0.376
Mortality at 3 months, n (%)	28/55 (50.9)	6/11 (54.6)	Odds Ratio	1.157 (0.316—4.243)	0.826	3.646 (0.184—72.275)	0.396
NIHSS at 3 months, median (IQR)	42 (5—42)	42 (0—42)	Beta	−1.756 (−15.762—12.251)	0.802	4.187 (−17.203—25.576)	0.690
Decompressive craniectomy, n (%)	6/136 (4.4)	0/62 (0)	——	——	0.180	——	——
Length of hospital stay, median (IQR) days	6 (3—14)	5 (3—10)	Beta	−3.761 (−6.577—−0.944)	**0.009**	−4.364 (−8.895—0.168)	0.059

Bold values indicate stasticially significant.
CI, confidence interval; mRS, modified Rankin scale; IQR, Interquartile range; NIHSS, National Institutes of Health Stroke Scale score.
*Adjusted for hypertension, atrial fibrillation, PVD, admission NIHSS, ASPECTS, tandem occlusion, and thrombectomy.

loss of patients to follow-up, which could be attributed to the high load of patients where priority was given to more severe cases. Lastly, because COVID-19 patients receive blood thinners as a part of their thromboprophylaxis, this may have protected them during the follow-up period from any new strokes or reocclusions that may have affected their functional outcome.[13]

Several factors play a role in the degree of recovery following a stroke, some of which are inherent to patients and others to stroke characteristics. Although adjusted for, our study demonstrated that unvaccinated patients had worse stroke characteristics on presentation compared to vaccinated patients in terms of tandem occlusion rates (11.5% vs. 2.0%; P = 0.062) which was comparable to the literature.[3,11] With respect to stroke care, the unvaccinated cohort underwent more mechanical thrombectomies which may be due to the higher rate of LVOs.

By catalyzing the conversion of angiotensin I and II to angiotensin (1—7), Angiotensin-converting enzyme 2 (ACE-2) mitigates the pro-inflammatory and pro-thrombotic effects of angiotensin II.[14] Because COVID-19 possess high tropism to ACE-2, its attachment via the spike protein to ACE-2 dysregulates the latter's effect on angiotensin II triggering inflammation, vasoconstriction, and a pro-coagulant state.[15] As a result, this pro-thrombotic milieu confers more stroke, LVOs, tandem occlusions, and multiple vessel occlusions. At a macro level, the complexity of strokes due to the high clot burden and consistency requiring longer procedure times and more number of passes, in addition to the higher frequency and incidence of strokes during the pandemic ultimately took a toll on health care systems.[16,17] To date, the Food and Drug Administration has approved the following 3 vaccines: 1) Comirnaty (BNT 162b2 mRNA vaccine) by Pfizer BionTech, 2) Ad26.COV2.S adenovirus vaccine by Johnson & Johnson/Janssen,[3] and Spikevax (mRNA-1273 vaccine) by Moderna.[18] All the approved vaccines are based on the full-length homotrimeric SARS-CoV-2 spike protein which plays a key role in the viral attachment to the ACE-2 receptor.[19,20] The messenger ribonucleic acid (mRNA) based vaccines (Pfizer and Moderna) consist of a lipid-enclosed nucleoside-modified mRNA encoding a different mutated spike protein, while the DNA-based vaccine (Janssen) consists of both a chimpanzee nonreplicating adenovirus and a type 26 nonreplicating recombinant adenovirus vector.[18,21] By creating a replica of COVID-19's spike protein, either by DNA or mRNA technology, vaccines promote the production of antibodies against COVID-19 and provide a strong immune reaction to destabilize the virus when an infection takes place.[21] Thus, at a micro level, vaccines decrease stroke severity by minimizing the pro-thrombotic and pro-inflammatory milieu of COVID-19

through mounting an immune response that limits COVID-19's effect on the ACE-2 receptor. Effectiveness and safety of vaccines in targeting the virus, diminishing it's spread, and minimizing its side effects have been demonstrated in several studies.[18,22-26]

Limitations

Conclusions of our work were limited by the retrospective nature of this single center study and the absence of randomization. Also, the loss of patients to follow-up may be a limiting factor of our mid-term results regarding functional outcome and mortality. This may have been due to either the high patient load health care systems that were faced with during the pandemic where priority was given to more severe cases or the retrospective nature of the study design. Furthermore, the small number of vaccinated patients limited the ability to compare the dose-dependent influence of vaccines on stroke outcome. Lastly, significant differences in baseline characteristics between both cohorts may have affected our outcomes; however, this confounding bias was controlled by adjustment.

CONCLUSIONS

The risk of stroke complicating infections with COVID-19 has been widely reported since the beginning of the pandemic. Our study showed that compared to the prepandemic era, stroke severity measured by the NIHSS score increased during the pandemic. Although vaccination did not show any significant difference in stroke patient outcomes on follow-up, vaccines were associated with lower rates of morbidity and mortality at discharge among COVID-positive stroke patients during the pandemic.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

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Conflict of interest statement: Dr. Jabbour is a consultant for Medtronic, MicroVention, Balt and Cerus Endovascular. Dr. Tjoumakaris is a consultant for Medtronic and MicroVention. Dr. Gooch is consultant for Stryker. The remaining authors have no conflicts to report.

Received 17 October 2022; accepted 29 November 2022

Citation: World Neurosurg. (2023) 170:e834-e839.
https://doi.org/10.1016/j.wneu.2022.11.132

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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