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.

COVID-19 and Stroke Recurrence by Subtypes: A Propensity-Score Matched Analyses of Stroke Subtypes in 44,994 Patients

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Background: Cerebrovascular diseases (CVDs), including varying strokes, can recur in patients upon coronavirus disease 2019 (COVID-19) diagnosis, but risk factor stratification based on stroke subtypes and outcomes is not well studied in large studies using propensity-score matching. We identified risk factors and stroke recurrence based on varying subtypes in patients with a prior CVD and COVID-19. *Methods:* We analyzed data from 45 health care organizations and created cohorts based on ICDs for varying stroke subtypes utilizing the TriNetX Analytics Network. We measured the odds ratios and risk differences of hospitalization, ICU/critical care services, intubation, mortality, and stroke recurrence in patients with COVID-19 compared to propensity-score matched cohorts without COVID-19 within 90-days. *Results:* 22,497 patients with a prior history of CVD within 10 years and COVID-19 diagnosis were identified. All cohorts with a previous CVD diagnosis had an increased risk of hospitalization, ICU, and mortality. Additionally, the data demonstrated that a history of ischemic stroke increased the risk for hemorrhagic stroke and transient ischemic attack (TIA) (OR:1.59, 1.75, p-value: 0.044*, 0.043*), but a history of hemorrhagic stroke was associated with a higher risk for hemorrhagic strokes only (ORs 3.2, 1.7, 1.7 and *p*-value: 0.001*, 0.028*, 0.001*). History of TIA was not associated with increased risk for subsequent strokes upon COVID-19 infection (all *p*-values: $\geq$ 0.05). *Conclusions:* COVID-19 was associated with an increased risk for hemorrhagic strokes and TIA among all ischemic stroke patients, an increased risk for hemorrhagic stroke in hemorrhagic stroke patients, and no associated increased risk for any subsequent strokes in TIA patients.

Keywords: COVID-19—Cerebrovascular disease—Ischemic stroke—Hemorrhagic stroke—Transient Ischemic attack—Cerebrovascular complication—Stroke recurrence

Introduction

Coronavirus disease 2019 (COVID-19), a recognized public health emergency of international concern, has posed diagnostics and treatment challenges, especially for patients with a prior history of cerebrovascular disease (CVD) and various neurological diseases.[1–5] It predominantly affects the respiratory system but has been observed to cause systemic inflammation, particularly inflammation of endothelial linings within the vascular system, resulting in CVDs, including varying strokes that can cause significant morbidity and mortality.[6–8] Although the risk of developing strokes such as ischemic and hemorrhagic strokes increases with age, comorbidities, and diminished immune response,[9] there are reported cases of younger patients with no significant comorbidities who suffered from strokes after contracting the virus.[10]

Studies have shown acute strokes following COVID-19 diagnosis,[6,11–14] and its accelerated progression upon infection.[15–17] Additionally, it has been demonstrated that any history of stroke and other CVDs are associated with increased in-hospital morbidity and mortality in

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COVID-19 patients, even when controlled for other comorbidities, such as hypertension and diabetes through propensity-score matching.[4,5,18] Currently, no studies have investigated the association of COVID-19 with stroke recurrence while distinguishing different stroke subtypes. Further studies are needed to understand COVID-19 as an independent risk factor for stroke recurrence. Since both COVID-19 and any prior history of CVDs are associated with stroke incidence, in the present study, we aimed to determine if COVID-19 is an independent risk factor for stroke recurrence based on varying subtypes in patients who have had a prior CVD diagnosis. We sought to investigate COVID-19 as a risk factor using different stroke subtypes (i.e., *individual International Classification of Diseases, Tenth Revision* (ICD-10) codes), which include hemorrhagic strokes, ischemic strokes, and transient ischemic attack (TIA).

Methods

We performed this retrospective study within a 90-day follow-up post-COVID-19 diagnosis by analyzing the de-identified TriNetX Analytics Network data. TriNetX is a global federated network comprised of data from electronic health records in 45 healthcare organizations in the U.S., totaling 53.8 million patients. The de-identified dataset does not provide data on individual hospitals and does not require institutional review board approval. The electronic medical encounters of 104,750 CVD patients older than 18 years between December 30th, 2010, and December 30th, 2020, were queried based on ICD-10 codes. (2021 data was not available when the authors conducted the study.) Specifically, ICD-10 codes to identify CVDs/stroke subtypes: non-traumatic subarachnoid hemorrhage (I60), non-traumatic intracerebral hemorrhage (I61), other and unspecified non-traumatic intracranial hemorrhage (I62), cerebral infarction (I63), occlusion, and stenosis of precerebral arteries, not resulting in cerebral infarction (I65), occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (I66), and other cerebrovascular diseases (I67).

The patient population was divided into 2 propensity-score matched cohorts based on a confirmed COVID-19 diagnosis at least 7 days after CVD diagnosis. The authors' recent publication provides the methodological details regarding the COVID-19 status determination.[5] To avoid overgeneralization and elucidate the differences in risk factors and associations, we compared 7 unique ICD-10 codes (I60, I61, I62, I63, I65, I66, and I67) to the respective propensity-score matched control cohort in separate analyses.

Statistical analysis

We used propensity-score matching to control confounding factors, such as age, sex, race, ethnicity, comorbidities such as essential/primary hypertension, type 2 diabetes mellitus, nicotine dependence, overweight/obesity, chronic kidney disease, atrial fibrillation/flutter, and asthma. A "caliper" of 0.1 pooled standard deviations of the propensity scores in aggregate was set to avoid matching patients with very different propensity scores. We created matched cohorts of patients with the same baseline characteristics, risk factors, and comorbidities. The control cohort consisted of a 1:1 propensity-score matched to each of the 7 previous cohorts except without COVID diagnosis within 90 days of a regular office visit (Z00.00: Encounter for general adult medical examination without abnormal findings). After propensity matching, 22,497 patients had CVD and a COVID-19 diagnosis, and 22,497 patients with CVD and no history of COVID-19. We performed this analysis to identify any significant differences in primary outcomes of CVD recurrence, hospitalization, ICU/critical care services, intubation, and mortality within 90 days of COVID-19 diagnosis. We calculated the odds ratios (ORs), relative ratios, and risk differences using the TriNetX platform. In particular, the z- test was used to evaluate the statistical significance of the risk difference. For groups with zero patients with adverse outcomes in the matched control cohort with a significant risk difference in the p-value, ORs are reported as inf. Statistical significance was set at a 2-sided $p < 0.05$.

Additionally, the TriNetX's "Number of Instances" analysis was used to compare the number of times a CVD occurred during the 90-day post-COVID-19 diagnosis or physician visit in the case of the control cohort. A T-test was performed on the number of instances of outcome per cohort (patients with zero instances were included in the mean). The study followed the STROBE guidelines.[19]

Results

Baseline characteristics of individual ICD-10 for CVD patients with and without COVID-19

There were 22,497 patients with a prior CVD diagnosis within 10 years and a confirmed COVID-19 diagnosis separated into 7 cohorts, and 22,497 patients in the respective propensity-score matched control cohorts without COVID-19 diagnosis. Supplemental Table 1 delineates the baseline characteristics for the individual ICD-10 cohorts for each CVD and their separate control cohorts without a COVID-19 diagnosis before propensity-score matching. Overall, in patients with a history of CVD, there were significantly more males, Black/African American, Hispanic/Latino, with type 2 diabetes or atrial fibrillation/flutter in the COVID-19 group than in the non-COVID-19 group (all p-values < 0.05).

Outcome comparison between individual ICD-10 for CVD patients with and without COVID-19

The adverse outcomes for patients with different CVDs and COVID-19, compared to matched control without

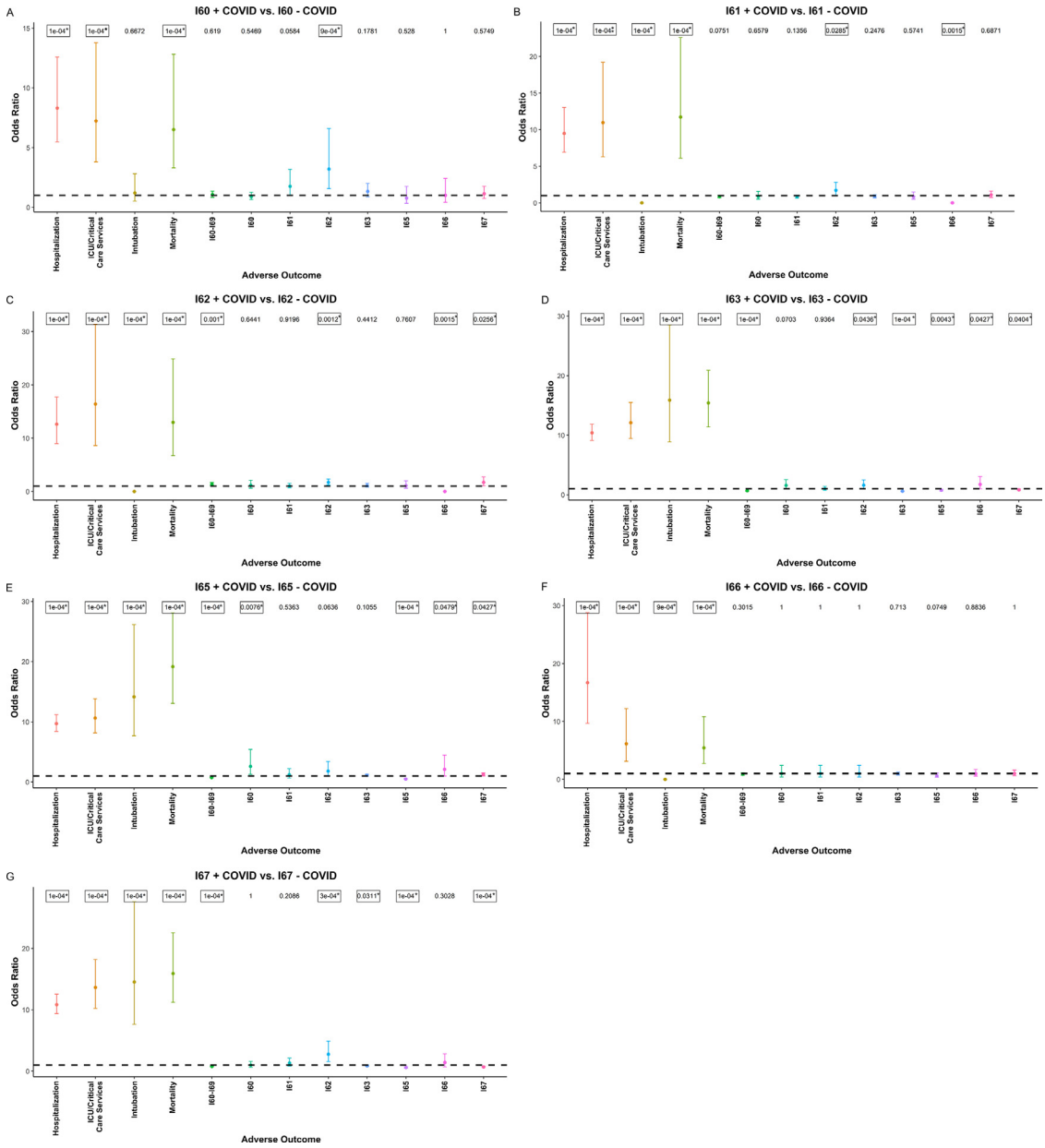

Fig. 1. *Outcome Analysis of (A) non-traumatic subarachnoid hemorrhage (I60) + COVID-19 vs. I60 - COVID-19, (B) non-traumatic intracerebral hemorrhage (I61) hemorrhage + COVID-19 vs. I61 - COVID-19, (C) other and unspecified non-traumatic intracranial hemorrhage (I62) + COVID-19 vs. I62 - COVID-19, (D) cerebral infarction (I63) + COVID-19 vs. I63 - COVID-19, (E) occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction (I65) + COVID-19 vs. I65 - COVID-19, (F) occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (I66) + COVID-19 vs. I66 - COVID-19, (G) other cerebrovascular diseases (I67) + COVID-19 vs. I67 - COVID-19. Numbers above the graph represent the* p*-values for each group; all significant* p*-values are denoted by * inside a box.*

COVID-19, are shown in Fig. 1 (the ORs with the error bars represent 95% confidence intervals (CI) with the risk difference *p*-values). Fig. 2 shows a heatmap of the ORs reported in Fig. 1 with significant outcomes denoted by a dot in the center. The associated details and numbers are described below and can be found in Table 1 and Supplemental Tables 2−8. Patient counts of 1−10 are reported as 10 by TriNetX to obfuscate patient and HCO identity.

Patients with a history of hemorrhagic (subarachnoid, intracerebral, intracranial hemorrhage) were at increased risk of intracranial hemorrhage (OR: 3.2, 1.7, 1.7, *p*-value: 0.001*, 0.028*, 0.001*) following COVID-19 diagnosis compared to non-COVID patients. Additionally, patients with a history of ischemic stroke (cerebral infarction) were at a lower risk of another ischemic stroke but a higher risk of hemorrhagic stroke and transient ischemic attack (TIA/occlusion and stenosis of cerebral arteries not resulting in infarction) with OR: 0.59, 1.59, 1.75, and *p*-value: < 0.0001*,0.044*, 0.043*. In patients with any history of stroke and TIA, the diagnosis of COVID-19

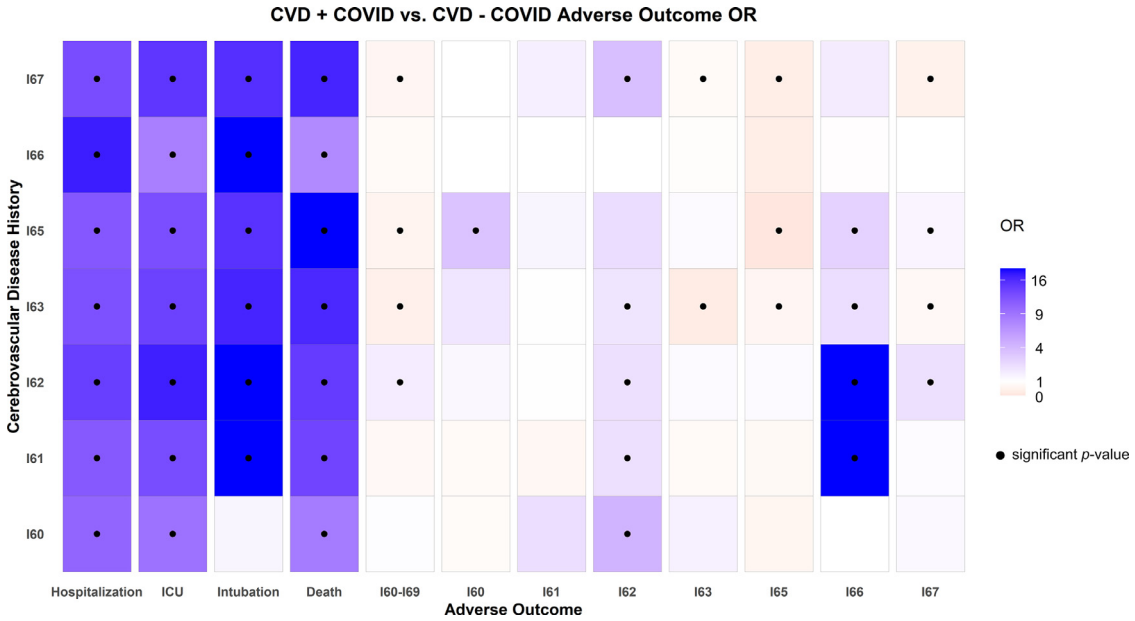

Fig. 2. *Heatmap of OR for adverse outcomes for individual ICDs with COVID-19 versus individual ICDs without COVID-19. The CVD ICDs include any CVD (I60–I69), nontraumatic subarachnoid hemorrhage (I60), nontraumatic intracerebral hemorrhage (I61), other and unspecified nontraumatic intracranial hemorrhage (I62), cerebral infarction (I63), occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction (I65), occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (I66), and other CVDs (I67). The colors represent the magnitudes of the ORs. Significant* p *values (<0.05) as calculated by the* z*-test based on the risk difference are characterized by a bold circle. CVDs: cerebrovascular diseases; ORs: odds ratios; COVID-19: coronavirus disease 2019.*

was associated with a significantly increased risk of hospitalization, ICU, intubation, and mortality compared to a matched control (Supplemental Tables 2−8).

Number of instances analysis for CVD recurrence in patients with and without COVID-19

We compared the association between COVID-19 and different stroke subtype recurrence in patients with a prior history using the number of instances of CVD in the groups mentioned above (within 90 days of confirmed COVID-19 diagnosis) to the matched control ICD cohorts without COVID-19 diagnosis (within 90 days of a regular office visit). Fig. 3 summarizes the "associated number of instances" described here. Patients in the I60 cohort with COVID-19 had significantly increased instances of any CVD and I62 (p-value = 0.025*, 0.003*). Patients in the I61 cohort with COVID-19 19 had significantly increased instances of I66 (p-value = 0.025*). Patients in the I62 cohort with COVID-19 had significantly increased instances of any CVD and I62 (p-value = < 0.0001*, 0.0004*). Patients in the I63 cohort had significantly decreased instances of I63 and I65 (p-value = < 0.0001*, 0.0084*). Patients in the I65 cohort had significantly increased instances of I62, I63, and I66 (p-value = 0.009*, 0.005*, 0.003*) and decreased instances of I65 (p-value = < 0.0001*). Patients in the I67 cohort had significantly increased instances of I62 (p-value = 0.012*) and decreased instances of I65 and I67 (p-value = 0.0001*, 0.013*)

Discussion

Various CNS manifestations, such as stroke, headache, impaired consciousness, delirium, and neuroleptic malignant syndrome, have been reported in patients with COVID-19.[20] We identified several significant findings from the study of 22,497 patients with different stroke subtypes within the past 10 years and COVID-19. Patients with COVID-19 were more likely to be male, Black/African American, and Hispanic. It has been shown that COVID-19 disproportionately affects racial and ethnic minority groups even when adjusted for common comorbidities and area deprivation index (ADI).[21,22] In our study, as also shown by others,[23−26] patients with COVID-19 had higher hospitalization rates, ICU, intubation, and mortality, regardless of the stroke subtype.

Patients with a history of ischemic stroke were at higher risk of developing hemorrhagic strokes and TIA within 90-days of COVID-19 diagnosis. However, patients with a history of hemorrhagic stroke were at higher risk for hemorrhagic strokes only and not TIA during the same period. Although associated with increased morbidity and mortality in our study, having a history of TIA did not increase the risk of subsequent strokes with COVID-19. Decreased public mobility during the pandemic can influence patients' decision to seek medical care when signs of TIA or acute ischemic strokes occur and bias the number of recorded TIA/ischemic stroke encounters.[2] Lazcano et al. reported that previous TIA is not associated with increased morbidity and

Table 1. *Adverse outcomes in CVD + COVID compared to control cohort of CVD − COVID.*

Outcome	I60	I61	I62	I63	I65	I66	I67
Hospitalization	8.304 (5.48−12.6)*	9.494 (6.9−13.06)*	12.62 (8.98−17.74)*	10.39 (9.124−11.841)*	9.703 (8.41−11.19)*	16.685 (9.673−28.78)*	10.842 (9.367−1548)*
ICU	7.234 (3.8−13.78)*	10.987 (6.29−19.2)*	16.416 (8.6−31.346)*	12.1 (9.451−15.49)*	10.628 (8.16−13.84)*	6.159 (3.106−12.213)*	13.641 (10.231-18.189)*
Intubation	1.204 (0.52−2.81)	inf	inf	15.88 (8.85−28.498)*	14.166 (7.673−26.15)*	inf	14.516 (7.637−27.591)*
Mortality	6.507 (3.3,12.83)*	11.734 (6.1−22.58)*	12.97 (6.76−24.9)*	15.42 (11.38−20.90)*	19.163 (13.071−28.096)*	5.428 (2.721−10.828)*	15.899 (11.212−22.546)*
Any CVD (I60-I69)	1.064 (0.83−1.36)	0.846 (0.7−1.02)	1.391 (1.143-1.694)*	0.699 (0.624-0.717)*	0.74 (0.68-0.81)*	0.875 (0.679-1.127)	0.782 (0.717-0.852)*
I60	0.901 (0.64−1.26)	0.877 (0.49−1.57)	1.153 (0.63−2.112)	1.559 (0.96−2.531)	2.607 (1.256−5.412)*	1 (0.413−2.423)	1 (0.633−1.579)
I61	1.758 (0.97−3.18)	0.816 (0.63−1.07)	1.021 (0.69−1.52)	1.013 (0.741−1.384)	1.211 (0.659−2.227)	1 (0.413−2.423)	1.336 (0.849−2.101)
I62	3.205 (1.56−6.6)*	1.724 (1.05−2.82)*	1.7 (1.23−2.35)*	1.585 (1.009−2.488)*	1.804 (0.959−3.394)	1 (0.413−2.423)	2.763 (1.557−4.901)*
I63	1.324 (0.88−1.99)	0.862 (0.67−1.11)	1.126 (0.83−1.52)	0.593 (0.549−0.641)*	1.121 (0.976−1.287)	0.947 (0.71−1.264)	0.874 (0.773−0.998)*
I65	0.766 (0.33−1.76)	0.854 (0.49−1.48)	1.097 (0.6−1.99)	0.78 (0.658−0.926)*	0.501 (0.448−0.561)*	0.631 (0.379−1.051)	0.617 (0.507−749)*
I66	1 (0.41−2.42)	inf	inf	1.754 (1.011−3.041)*	2.104 (0.99−4.472)	0.958 (0.54−1.701)	1.43 (0.722−2.834)
I67	1.134(0.73−1.76)	1.085 (0.73−1.61)	1.709 (1.06−2.75)*	0.845 (0.719−0.993)*	1.235 (1.01−1.52)*	1 (0.627−1.595)	0.699 (0.618−0.791)*

Odds Ratio and 95% confidence interval of severe outcomes and subsequent CVD for non-traumatic subarachnoid hemorrhage (I60), non-traumatic intracerebral hemorrhage (I61), other and unspecified non-traumatic intracranial hemorrhage (I62), cerebral infarction (I63), occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction (I65), occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (I66), and other cerebrovascular diseases (I67) compared to control cohort of patients with CVD and no COVID-19 diagnosis. For comparisons with zero patients with adverse outcomes in the matched control cohort with a significant risk difference *p*-value, ORs are reported as inf.

mortality after COVID-19, unlike ischemic and hemorrhagic strokes.[4] Additionally, Katz et al., in a retrospective case series, observed that symptomatic COVID-19 patients with ischemic strokes had 31.7% rate of simultaneous intracranial hemorrhage.[25] SARS-CoV-2 engages angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell,[27] which leads to the degradation of ACE2 receptors and accumulation of angiotensin 2 in the blood, which may be linked to the occurrence of hemorrhagic stroke.

While stroke has been shown to occur commonly in patients with COVID-19 diagnosis[6,28,29], which could have multifactorial etiology, there hasn't been a propensity-matched study differentiating stroke subtypes to understand whether recurrences of different stroke subtypes are independently associated with COVID-19 diagnosis in those with a prior history. Our study is the first propensity-score matched analysis to analyze the influence of each stroke subtype on the recurrence rate specified by the subtype in the COVID-19 population within 90-days of COVID-19 diagnosis. Our number of instance analyses demonstrated that patients with a history of hemorrhagic stroke have significantly higher instances of hemorrhagic stroke events but not ischemic stroke events than their propensity-matched control cohort without COVID-19. Additionally, patients with a history of ischemic stroke have a significantly lower number of instances where ischemic strokes were reported during the 90 days. Patients with TIA did not differ in any stroke subtype in the number of instances analysis compared to those without COVID-19.

Prior ischemic or hemorrhagic strokes may potentially trigger intraparenchymal long-lasting damage, such as microbleeds and hemorrhagic lesions that can lead to generalized endotheliali tis resulting in increased susceptibility for disseminated intravascular coagulation and a prothrombotic state.[30,31] Our observed higher rates of stroke instances in patients with a previous history are essential since they make up 6.09% of the reported COVID-19 cases within the TriNetX Network. It is important to note that in the setting of hospital admission, especially in peak phases of the outbreak, the risk factor identification/stratification could often be delayed or missed. Therefore, vigilant stroke monitoring is essential in patients with a prior history to prevent irreversible damages, increased length of hospital stay, and poor prognosis.

Our study has several limitations. As previously reported,[5] secondary COVID-19 infections cannot be accounted for during the 90 days outcome period due to the database structure. Additionally, despite using propensity-score matching, there are unknown confounding variables, especially socioeconomic factors and access to medical care. Furthermore, stroke subtypes can occasionally be misclassified during data entry, introducing a bias. Despite all this, stroke is a heterogeneous disease.

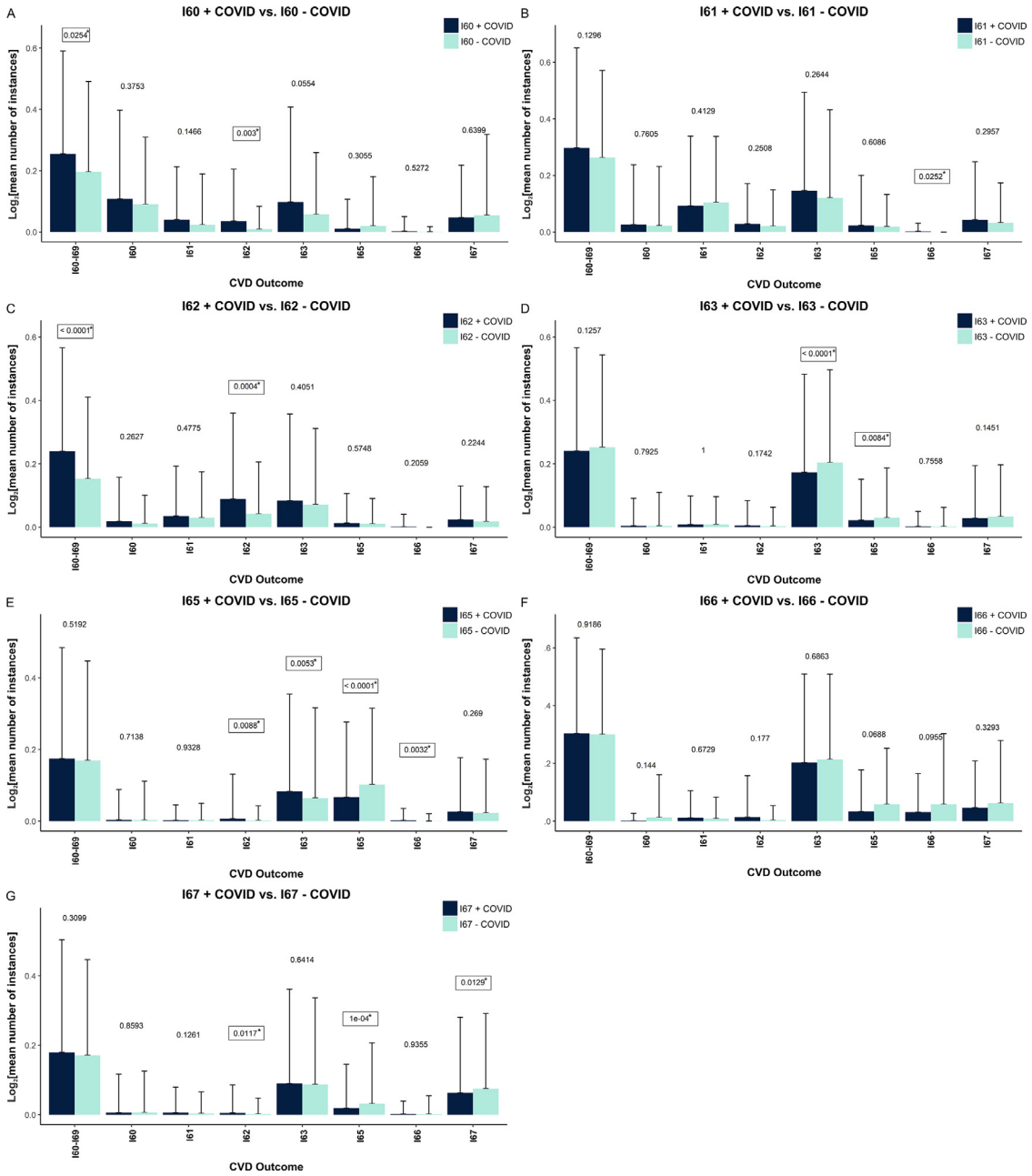

Fig. 3. *Number of instances for cerebrovascular diseases of (A) non-traumatic subarachnoid hemorrhage (I60) + COVID-19 vs. I60 - COVID-19, (B) non-traumatic intracerebral hemorrhage (I61) hemorrhage + COVID-19 vs. I61 - COVID-19, (C) other and unspecified non-traumatic intracranial hemorrhage (I62) + COVID-19 vs. I62 - COVID-19, (D) cerebral infarction (I63) + COVID-19 vs. I63 - COVID-19, (E) occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction (I65) + COVID-19 vs. I65 - COVID-19, (F) occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (I66) + COVID-19 vs. I66 - COVID-19, (G) other cerebrovascular diseases (I67) + COVID-19 vs. I67 - COVID-19. Numbers above the graph represent the* p*-values for each group; all significant* p*-values are denoted by * inside a box.*

Different subtypes have unique underlying pathophysiological processes that contribute to prognosis. Our study gives insight into the role of varying stroke subtypes on recurrence type and rate and associated morbidity and mortality. Further studies stratifying socioeconomic factors, asymptomatic cases, and final cause of death are imperative to expand knowledge on this issue.

Conclusion

In patients with a history of stroke of any subtype, COVID-19 is independently associated with increased hospitalization, ICU, intubation, and mortality compared with propensity-score matched control without COVID-19. COVID-19 was associated with an increased risk of

hemorrhagic strokes and TIA among all ischemic stroke patients. Patients with a history of hemorrhagic strokes were at an overall increased risk of hemorrhagic strokes within 90-days post-COVID-19. History of TIA was not associated with an increased risk of any subsequent strokes.

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Declaration of Competing Interest

All authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106591.

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