Global Impact of the COVID-19 Pandemic on Cerebral Venous Thrombosis and Mortality

SVIN COVID-19 Global COVID Stroke Registry

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Original Article

Global Impact of the COVID-19 Pandemic on Cerebral Venous Thrombosis and Mortality

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Background and Purpose Recent studies suggested an increased incidence of cerebral venous thrombosis (CVT) during the coronavirus disease 2019 (COVID-19) pandemic. We evaluated the volume of CVT hospitalization and in-hospital mortality during the 1st year of the COVID-19 pandemic compared to the preceding year.

Methods We conducted a cross-sectional retrospective study of 171 stroke centers from 49 countries. We recorded COVID-19 admission volumes, CVT hospitalization, and CVT in-hospital mortality from January 1, 2019, to May 31, 2021. CVT diagnoses were identified by International Classification of Disease-10 (ICD-10) codes or stroke databases. We additionally sought to compare the same metrics in the first 5 months of 2021 compared to the corresponding months in 2019 and 2020 (ClinicalTrials.gov Identifier: NCT04934020).

Results There were 2,313 CVT admissions across the 1-year pre-pandemic (2019) and pandemic year (2020); no differences in CVT volume or CVT mortality were observed. During the first 5 months of 2021, there was an increase in CVT volumes compared to 2019 (27.5%; 95% confidence

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interval [CI], 24.2 to 32.0; *P*<0.0001) and 2020 (41.4%; 95% CI, 37.0 to 46.0; *P*<0.0001). A COVID-19 diagnosis was present in 7.6% (132/1,738) of CVT hospitalizations. CVT was present in 0.04% (103/292,080) of COVID-19 hospitalizations. During the first pandemic year, CVT mortality was higher in patients who were COVID positive compared to COVID negative patients (8/53 [15.0%] vs. 41/910 [4.5%], *P*=0.004). There was an increase in CVT mortality during the first 5 months of pandemic years 2020 and 2021 compared to the first 5 months of the pre-pandemic year 2019 (2019 vs. 2020: 2.26% vs. 4.74%, *P*=0.05; 2019 vs. 2021: 2.26% vs. 4.99%, *P*=0.03). In the first 5 months of 2021, there were 26 cases of vaccine-induced immune thrombotic thrombocytopenia (VITT), resulting in six deaths.

Conclusions During the 1st year of the COVID-19 pandemic, CVT hospitalization volume and CVT in-hospital mortality did not change compared to the prior year. COVID-19 diagnosis was associated with higher CVT in-hospital mortality. During the first 5 months of 2021, there was an increase in CVT hospitalization volume and increase in CVT-related mortality, partially attributable to VITT.

Keywords COVID-19; Cerebral venous thrombosis; Vaccine-induced immune thrombotic thrombocytopenia; Mortality; SARS-CoV-2; Stroke

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Introduction

Since the first case in December 2019, coronavirus disease 2019 (COVID-19) has been responsible for more than 340 million infections and over 5.5 million deaths.[1] Though most of the morbidity and mortality associated with COVID-19 is related to pulmonary complications, the disease has had wide-ranging systemic effects, including a range of neurological manifestations[2,3] and disruption of coagulation homeostasis.[4-7] This disruption in normal coagulation may trigger abnormal clotting events such as venous thromboembolism and stroke.[8-10]

Cerebral venous thrombosis (CVT) is a rare cause of stroke caused by the formation of clots in the brain's venous system. The incidence of CVT has been reported to increase over the last decade, either from changing risk factors or improved detection.[11-13] Compared to other forms of stroke, the incidence of CVT is more common in younger patients and women. CVT generally has a favorable prognosis with a good 90-day neurological outcome seen in greater than 80% of patients.[14-16]

Several regional and multicenter reports described an increase in the incidence of CVT and severity of CVT during the COVID-19 pandemic.[6,17] In February of 2021, reports emerged of CVT following COVID-19 vaccination with adenovirus-based vaccines. In these patients, a syndrome characterized by thrombosis, thrombocytopenia,[18] and antibodies to platelet factor 4 were observed and the syndrome was termed vaccine-induced immune thrombotic thrombocytopenia (VITT).[19-21] Whereas the relative changes in stroke[22-26] and subarachnoid hemorrhage volumes[27] have been described during the first wave of the COVID-19 pandemic, the low incidence of CVT has limited studies during the COVID-19 pandemic. At present, there is insufficient data to determine whether CVT incidence or mortality changed during the COVID-19 pandemic.

The primary objectives of this study were to evaluate changes in the volume of CVT hospitalizations and CVT in-hospital mortality during the 1st year of the COVID-19 pandemic (January 1, 2020, to February 28, 2021) compared to the preceding year (January 1, 2019, to February 29, 2020), adjusting for the beginning of the pandemic month in each country. The secondary objective of this study was to examine the association between the volume of COVID-19 admissions and the volume of CVT hospitalizations. An additional objective of this study was to evaluate whether CVT in COVID-19 positive patients was associated with increased risk of in-hospital mortality in the 1st year of the pandemic.

Methods

Hypothesis

Our primary hypothesis was that there would be an increase in the rate of CVT hospitalizations or CVT in-hospital mortality between the 1st year of the COVID-19 pandemic and the preceding year. Our secondary hypothesis was that there would be no association between the burden of COVID-19 admissions and CVT hospitalizations. Furthermore, given the higher mortality observed in ischemic stroke patients with COVID-19,[28] we hypothesized that CVT hospitalization in a COVID-19 patient would confer a higher risk of mortality compared to a patient

without COVID-19.

Study design

We conducted a cross-sectional study evaluating the monthly volumes and mortality of consecutive patients hospitalized with a diagnosis of CVT or COVID-19 from January 1, 2019 to May 31, 2021. Case ascertainment was verified by a physician, stroke, or research coordinator at each site. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Supplementary Table 1).

Setting and participants

Data were collected from collaborators of the Society of Vascular and Interventional Neurology, the European Stroke Organization, the Middle East North Africa Stroke and Interventional Neurotherapies Organization, the Japan Society of Vascular and Interventional Neurology, the Latin America Stroke Group, and additional academic partners. Of 450 centers invited to participate in this global study of the impact of COVID-19 on cerebrovascular disease (including stroke, CVT, and subarachnoid hemorrhage), data were received from 275 centers. Of these 275 centers, 177 centers submitted data related to CVT. There were six centers with missing data prior to the COVID-19 pandemic, yielding 171 centers across six continents and 49 countries for the CVT analysis. For some months, there was missing CVT data from eight centers, yielding 163 centers for the 1-year volume comparative analysis (Figure 1). The study size was based on the number of submitted cases with complete data for each variable.

Comprehensive stroke centers (CSC) were defined by the availability of mechanical thrombectomy for ischemic stroke on January 1, 2019. All other centers were defined as primary stroke centers (PSC). Centers were divided into tertiles (low, intermediate, high) by COVID-19 monthly hospitalization volume (Supplementary Table 2).

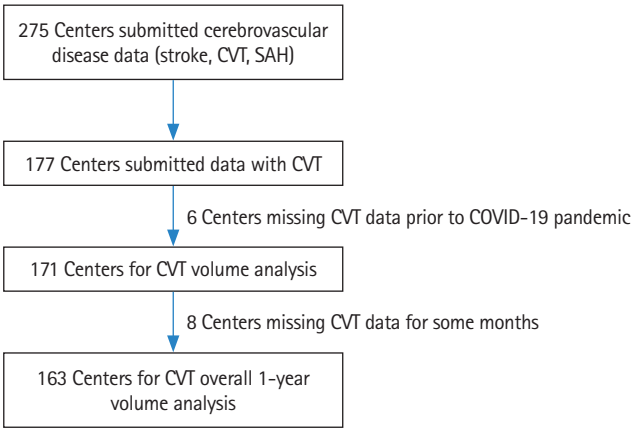

Figure 1. Study flow chart. CVT, cerebral venous thrombosis; SAH, subarachnoid hemorrhage; COVID-19, coronavirus disease 2019.

The start date of the pandemic in each country was determined as the date of the first reported case of COVID-19 (Supplementary Table 3). We defined the second wave of the COVID-19 pandemic using a minimum doubling of case volume following a >50% decline in case volume from the previous wave's peak. The start date for this occurrence was chosen as the case volume minimum closest to the second wave (Supplementary Table 3).[29] The study's primary data collection was conducted between May 1, 2021 and September 15, 2021. Follow-up queries to sites were completed by January 1, 2022.

Study variables and outcome measures

We collected monthly CVT hospitalization volume, CVT in-hospital mortality, and COVID-19 hospitalization volume. For patients hospitalized with CVT, the diagnosis had to be confirmed by neuroimaging with computed tomography venogram or magnetic resonance venogram. We recorded whether the CVT patient had concomitant COVID-19; we also collected thrombocytopenia status. CVT hospitalizations were identified using International Classification of Disease-10 (ICD-10) codes or prospectively maintained stroke databases. The following ICD-10 codes were used: G08 (intracranial phlebitis and thrombophlebitis), I63.6 (cerebral infarction due to CVT, nonpyogenic), I67.6 (nonpyogenic thrombosis of intracranial venous system), O22.5 (CVT in pregnancy). COVID-19 hospitalization was defined as any patient admitted with COVID-19 diagnosis to a participating center, including those without any neurologic diagnosis, utilizing ICD-10 code U07.1. Cases of confirmed or probable VITT were identified using the American Society of Hematology definitive diagnostic criteria.[30] Confirmed cases met all five criteria and probable cases met clinical criteria with incomplete laboratory testing.

Standard protocol approvals, registrations, and patient consents

This was an investigator-initiated study. The Institutional Review Boards (IRBs) from the coordinating sites (Emory University and Boston Medical Center) considered that the investigators did not have access to protected health information in this follow-up study, and thus no IRB oversight was required since the study did not meet the United States federal description of human subject research. Investigators sought local IRB or ethics approval when required by local regulations. Informed consent was waived because of the retrospective nature of this study and because the research was considered no more than

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minimal risk. The study was registered under NCT04934020.

Bias

Data verification was conducted by the lead author (T.N.N.) following submission by sites. In order to fully capture volume and mortality data, data collection was completed more than 3 months after the last date of patient inclusion to avoid incomplete data bias with any lag in data reporting. Centers contributing data within a stroke network were instructed to include transfer patients from the site of initial evaluation only. In nations with either consistently high COVID-19 case volumes or consistently near-zero case volumes, pandemic waves were obscured and not well captured.

Statistical analysis

We compared percentage change in the absolute number of CVT admissions for the following periods: (1) before and during the COVID-19 pandemic and (2) first 5 months of 2019 vs. 2020, 2019 vs. 2021, and 2020 vs. 2021. The 95% confidence intervals (CIs) for percentage change were calculated using the Wilson procedure without correction for continuity. The differences in admissions across the two periods were assessed for significance using the Poisson means test. The analysis was repeated by stroke center (primary or comprehensive) and hospital COVID-19 volume (low, intermediate, or high). The relative percentage decrease in volume between different categories (for example, low vs. intermediate hospital volume) was tested

Table 1. Cerebral venous sinus thrombosis admissions: overall 1-year and monthly volumes before and during the COVID-19 pandemic

Variable	Overall volume					Monthly volume*			
	No. of hospital	No.†	No.‡	Change	*P*	No. of hospital	Before COVID-19	During COVID-19	*P*
Overall	163	1,139	1,174	3.1 (2.2–4.2)	0.47	171	0.60±0.12	0.61±0.12	0.97
Primary vs. comprehensive stroke center§									
Primary	39	201	229	13.9 (9.8–19.4)	0.18	42	0.52±0.16	0.57±0.18	0.20
Comprehensive	124	938	945	0.7 (0.4–1.5)	0.87	129	0.70±0.18	0.69±0.17	0.66
Center COVID-19 volume‖									
Low	51	216	246	13.9 (9.9–19.1)	0.16	52	0.50±0.12	0.55±0.13	0.11
Intermediate	50	267	312	16.9 (12.8–21.8)	0.06	50	0.39±0.21	0.47±0.21	0.07
High	49	536	509	−5.0 (−7.2 to −3.5)	0.40	52	1.07±0.26	1.02±0.26	0.43

Values are presented as percentage (95% confidence interval) or adjusted mean±standard error.
COVID-19, coronavirus disease 2019.
*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent; †Number of admissions during 12 months before the COVID-19 pandemic; ‡Number of admissions during 12 months of COVID-19 pandemic; §Primary vs. Comprehensive, $P<0.0001$; ‖Low vs. Intermediate ($P=0.366$), Low vs. High (P=not available), Intermediate vs. High (P=not available).

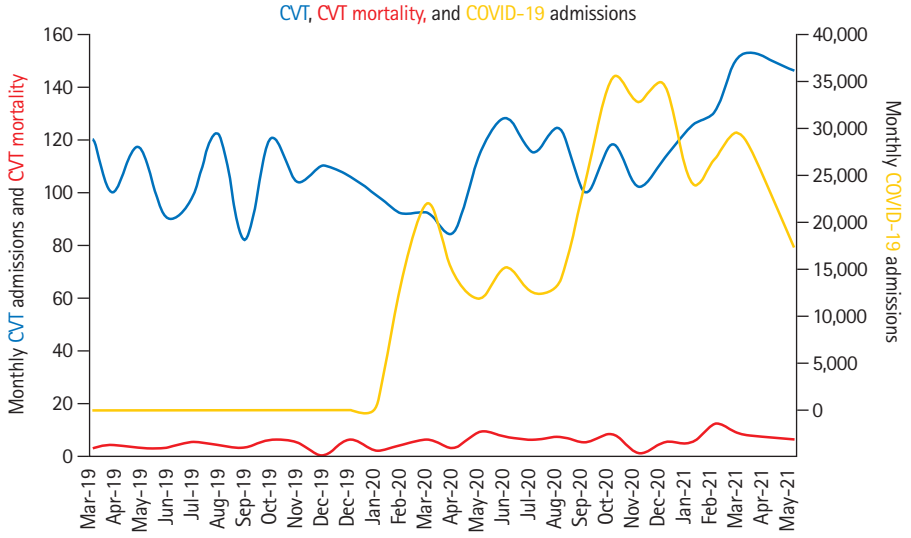

Figure 2. Cerebral venous thrombosis (CVT), CVT mortality, and coronavirus disease 2019 (COVID-19) admissions. CVT admissions are based on data submitted from 171 centers. COVID-19 admissions are based on data submitted from 154/171 centers.

using the z-test of proportion.

In addition to absolute volume analysis, we also compared average monthly volumes (admissions/month) of CVT admissions for the aforementioned periods. The data were analyzed in a mixed design using a repeated-measures analysis of variance (PROC MIXED analysis in SAS) accounting for the paired data structure and potential covariates. The unstructured matrix was the best fit and used for the analyses. The monthly hospital volume analysis was adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent. Estimated marginal means were calculated using the least square means (LSMEANS) statement in PROC MIXED. Like the overall volume analysis, monthly volume analysis was stratified by stroke center and COVID-19 volume.

Finally, we compared CVT in-hospital mortality rate (CVT mortality/CVT admissions) before and during the COVID-19 pandemic and for the first 5 months of 2019, 2020, and 2021 using the chi-square test. The difference in in-hospital mortality in CVT patients with or without concomitant COVID-19 was also tested using the chi-square test. All data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at a *P*-value of <0.05.

Data availability

Data are available upon reasonable request to the corresponding author.

Results

Across the study period from January 1, 2019 to May 31, 2021, there were 3,210 CVT hospitalizations and 329,042 COVID-19 admissions across 171 centers. During the 1st year of the COVID-19 pandemic from January 1, 2020, to February 28, 2021 (adjusting for the month in which the pandemic began in each country), there were 217,560 COVID-19 hospitalizations across 154 of 171 centers that submitted CVT and COVID data. There were 2,313 CVT admissions across the pandemic and pre-pandemic years (Table 1 and Figure 2).

CVT hospitalization volume

Over the 1 year of the COVID-19 pandemic, there was no difference in overall CVT hospitalization volume compared to the prior year (pre-pandemic 1,139 vs. pandemic 1,174; 3.1%; 95% CI, 2.2 to 4.2; *P*=0.47). No difference was observed in overall monthly volume before and during the COVID-19 pandemic (0.60 vs. 0.61, *P*=0.97), adjusting for the date of peak COVID-19 cases by country, date of the start of the second wave, and

Table 2. CVT in-hospital mortality rate 1 year prior compared to 1 year during the COVID-19 pandemic

Variable	No. of hospital	CVT admissions	CVT mortality	Mortality rate (%)	*P*
Overall					
Before COVID-19	138	1,013	35	3.46	0.12
During COVID-19		1,037	50	4.82	
Primary stroke centers					
Before COVID-19	37	196	8	4.08	0.25
During COVID-19		226	15	6.64	
Comprehensive stroke centers					
Before COVID-19	101	817	27	3.30	0.29
During COVID-19		811	35	4.32	
Center COVID-19 volume: low					
Before COVID-19	43	199	6	3.02	0.42
During COVID-19		221	10	4.52	
Center COVID-19 volume: intermediate					
Before COVID-19	42	243	10	4.12	1.00
During COVID-19		267	11	4.12	
Center COVID-19 volume: high					
Before COVID-19	44	483	19	3.93	0.23
During COVID-19		464	26	5.60	

The before COVID-19 period was the 12 months immediately preceding the during COVID-19 period.
COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis.

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continent. Across subgroups of PSC versus CSC, COVID-19 hospitalization tertiles, there was no difference in overall or monthly CVT volume. However, the increase in CVT hospitalization volume at PSC was greater than at CSC (13.9% vs. 0.7%, *P*<0.0001) (Table 1).

During the first wave of the pandemic in 2020, there was a decrease in CVT monthly adjusted volumes when comparing the first 5 months of 2020 to the first 5 months of 2019 (0.65 vs. 0.55, *P*=0.03). For the overall 5-month volume, absolute declines were observed in all subgroups but were non-significant (Supplementary Table 4). In contrast, during the first 5 months of 2021, there was a significant increase in overall CVT volumes compared to the first 5 months of both 2019 (27.5%; 95% CI, 24.2 to 32.0; *P*<0.0001) (Supplementary Table 5) and 2020 (41.4%; 95% CI, 37.0 to 46.0; *P*<0.0001) (Supplementary Table 6). When comparing 2021 to 2020, significantly increased overall volumes were observed across all subgroups with no differences between subgroups. When comparing 2021 to 2019, increased CVT volumes were observed at CSC (31.3%; 95% CI, 26.8 to 36.1; *P*<0.0001) but not at PSC (14.9%; 95% CI, 9.5 to 22.6; *P*=0.28).

CVT mortality

A hundred and forty centers provided mortality data, among which 138 had complete information on CVT admissions. The in-hospital mortality rate was 3.46% (35/1,013) among CVT admissions in the year pre-pandemic compared to 4.82% (50/1,037) among CVT admissions during the first pandemic year, representing a non-significant change in mortality during the pandemic (*P*=0.12). No significant differences were observed within or between any subgroup (Table 2).

There was a statistically significant increase in CVT mortality during the first 5 months of pandemic years 2020 and 2021 when compared to the first 5 months of the pre-pandemic year 2019 (2019 vs. 2020: 2.26% vs. 4.74%, *P*=0.05; 2019 vs. 2021: 2.26% vs. 4.99%, *P*=0.03) (Figure 3). However, no difference in CVT mortality was noted between the first 5 months of the 2020 and 2021 (first 2 pandemic years).

During the initial 5 months of 2021, we identified 26 (18 confirmed, eight probable cases) of VITT, resulting in six deaths (three confirmed VITT, three probable VITT) at a case fatality rate of 23.08%. Excluding the VITT cases, the CVT mortality rate during the first 5 months of 2021 dropped from 4.99% to 4.04% (*P*=0.12) (Figure 3), resulting in a non-significant difference in CVT-related mortality between these months and the corresponding months of the pre-pandemic year.

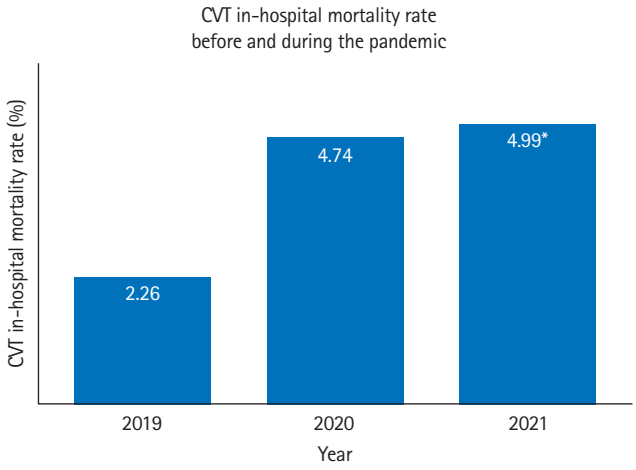

Figure 3. Cerebral venous thrombosis (CVT) in-hospital mortality rate during the first 5 months of three different year (2019, 2020, 2021) comparisons in 138 hospitals with complete CVT mortality and CVT admission data. CVT in-hospital mortality 2019 vs. 2020: 2.26% vs. 4.74%, *P*=0.05; CVT in-hospital mortality 2019 vs. 2021: 2.26% vs. 4.99%, *P*=0.03; CVT in-hospital mortality 2020 vs. 2021, no difference. *Twenty-six vaccine-induced immune thrombotic thrombocytopenia (VITT) probable or confirmed cases were identified in 2021, resulting in six deaths. Excluding cases of confirmed or probable VITT, the case fatality rate of CVT during the first 5 months of 2021 drops from 4.99% to 4.04% (20/495 CVT cases) (*P*=0.1).

CVT and COVID-19 diagnosis

There were 163 centers that reported CVT patients with concomitant COVID-19 diagnoses. During the first pandemic year through May 2021, COVID-19 diagnosis with CVT admission was present in 7.6% (132/1,738) of patients with continental variation: Africa 25.0% (13/52), Asia 5.5% (28/511), North America 3.0% (15/509), South America 13.4% (15/112), and Oceania 0% (0/25) (Supplementary Table 7). There were 154 centers that reported COVID-19 and CVT hospitalization. Of 292,080 COVID-19 hospitalizations, CVT was present in 103 patients (0.04%) (Supplementary Table 8).

CVT mortality and COVID

During the first 12 months of the pandemic, adjusted for the starting month of the pandemic by country, 120 centers from 41 countries reported CVT and COVID-19 incidence rates, and CVT mortality. There were 963 CVT patients in the 1st year of the COVID-19 pandemic, of which 910 were COVID-19 negative, and 53 had COVID-19. CVT mortality was higher in the COVID-19 patients compared to COVID-19 negative group (8/53 [15%] vs. 41/910 [4.5%], *P*=0.004) (Supplementary Table 9).

Discussion

In this large, multinational longitudinal cross-sectional study, we observed no significant differences in CVT volume or CVT in-hospital mortality overall, or any subgroup, between the 1st

year of the COVID-19 pandemic compared to the prior year. In contrast, higher CVT in-hospital mortality was noted during the first 5 months of the pandemic for 2020 and 2021 than the equivalent months in 2019. During the 1st year of the pandemic, patients with CVT who were COVID positive had higher in-hospital mortality than COVID negative patients. Differences in the year-over-year CVT volume and mortality were observed between comprehensive and PSC. PSC had greater absolute increases for CVT volume than CSC.

No difference in CVT volume was observed between the 1st year of the pandemic, the first 5 months of the pandemic, and the prior year equivalent period. However, reduced volumes have been observed in other forms of stroke over the same time period.[31,32] In this context, the preservation of CVT volumes may represent a relative increase in CVT incidence, masked by decreased patient presentations for stroke overall. Moreover, the increase in CVT in-hospital mortality during the first 5 months of the COVID-19 pandemic may suggest that patients with milder CVT did not present to stroke centers during the COVID-19 pandemic. Since more than 80% of patients with CVT will have a favorable neurological outcome,[14] patients with milder CVT and particularly those with isolated headache may have been less likely to present in a delayed fashion for persisting deficits and may have been missed altogether.

In order to evaluate differences between the early stage of the pandemic, later stages of the pandemic, and pre-pandemic, we compared the first 5 months of 2019, 2020, and 2021. When comparing 2019 to 2020, monthly adjusted CVT volumes decreased though overall 5-month volumes were not significantly decreased and CVT in-hospital mortality was increased. During the early stage of the pandemic, the decrease in CVT volume was similar in magnitude to that seen for overall stroke volume decline in the first wave or first 4 months of the COVID-19 pandemic.[23] The observation of significantly decreased CVT volumes during the initial months of 2020 but unchanged volumes for the entire year suggests differential presentation of CVT patients during the early stage of the pandemic.

An increase in CVT in-hospital mortality was observed in the first 5 months of 2020 as compared to the equivalent pre-pandemic period in 2019 (2.26% vs. 4.74%, P=0.05), which may be attributed to concomitant COVID infection during the pandemic (Supplementary Table 7) or a higher severity of CVT disease presentation during the initial pandemic months. The large increase in diagnosis and CVT in-hospital mortality during the first 5 months of 2021 suggests a substantially different patient population compared to previous years. This difference is likely explained by increased vigilance by both the public and medical community following the discovery of VITT. One single-center study reported a 262% increase in non-invasive venograms performed during the 3 weeks following the Ad.26.COV2.S vaccine administration pause in the United States compared to the same period in previous years and that patients were less likely to have classic symptoms of CVT.[33]

During the initial months of 2021, we identified 26 confirmed or probable cases of VITT, resulting in six deaths, a case fatality rate of 23%. Excluding cases of confirmed or probable VITT, the case fatality rate of CVT during the first 5 months of 2021 dropped from 4.99% to 4.04%, suggesting VITT is an important factor contributing to the overall rise in CVT mortality during the first 5 months of 2021.

Our results contrast with previous studies indicating a potential increase in both CVT volume and mortality[34] during the COVID-19 pandemic. These previous studies were smaller, focused on patients with COVID-19 and concomitant CVT,[9,17,35,36] and captured fewer CVT events than were observed in our study. The low incidence of CVT and lack of a control group of CVT patients prior to the pandemic limit the scope of prior studies. The lack of statistical significance in the mortality outcome of this study, despite a nearly 40% absolute increase, underscores the difficulty in studying CVT given its overall rarity. Additionally, we observed no difference in monthly CVT volumes during the COVID-19 pandemic when adjusting for the continent, COVID-19 volumes, and wave start dates. A previous large study of electronic health record data found an increase in CVT rates among those with COVID-19 infection compared to matched cohorts who had either received an mRNA vaccine or had an influenza infection. However, that study captured nearly 100 times fewer CVT events (23 vs. 2,274) and it is unclear whether the included population is representative.[37]

During the 1st year of the pandemic, among patients with CVT and COVID-19, we noted a higher in-hospital mortality rate than patients who were COVID negative (15% vs. 4.5%, P=0.004). While we could not control for confounding factors, this relationship may be biologically plausible given that concomitant COVID-19 infection has been well documented to be associated with higher mortality in ischemic stroke patients.[38,39] To our knowledge, this is the first study to demonstrate the relationship between COVID-19 and increased CVT in-hospital mortality across a large, multinational CVT cohort.

While our study demonstrated no differences in CVT volumes or mortality during the 1st year of the COVID-19 pandemic in a large multinational sample, we drew our sample only from stroke centers. Diagnosis of CVT requires advanced imaging, and the availability of such imaging is country and center-de-

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pendent.[40,41] Any shift of patients towards presenting at non-stroke-centers is likely to lead to reduced CVT diagnosis. Due to the cross-sectional nature of this study, we were limited in our ability to investigate patient-level data. As a result, we cannot determine changes in CVT severity between time periods that did not result in a mortality difference. Further research is necessary to investigate any changes in the clinical characteristics of CVT during the COVID-19 pandemic.

Conclusions

No differences in CVT volume or mortality were observed during the 1st year of the COVID-19 pandemic compared to the prior year. During the 1st year of the pandemic, there was higher in-hospital mortality in patients with CVT who were COVID positive compared to COVID negative. A non-significant absolute increase in mortality may be attributable to the emergence of VITT and differences in patient presentation patterns during the pandemic.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2022.00752.

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Supplementary Table 1. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item no.	Recommendation	Page no.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1,2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4,5
		(b) Describe any methods used to examine subgroups and interactions	4
		(c) Explain how missing data were addressed	3
		(d) Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	4,5
		(e) Describe any sensitivity analyses	NA
Results			
Participants Descriptive data	13	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) Cohort study—Summarise follow-up time (e.g., average and total amount)	6
Outcome data	15	Cohort study—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	4,5,6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	4,5
Discussion			
Key results	18	Summarise key results with reference to study objectives	6,7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7,8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7,8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; NA, not available.

Supplementary Table 2. Threshold values for monthly volume tertiles for COVID-19 admissions

	Low	Intermediate	High
COVID-19 admissions	≤17.9	>17.9–≤115.1	>115.1

COVID-19, coronavirus disease 2019.

Supplementary Table 3. Timeline of first reported cases, 1st wave peak, and 2nd wave peak by country

Country	1st reported case*	1st wave peak	Second wave date†
Argentina	3/3/2020	10/21/2020	12/11/2020
Australia	1/25/2020	3/20/2020	6/9/2020
Austria	2/25/2020	3/28/2020	6/30/2020
Bangladesh	3/8/2020	7/2/2020	2/24/2021
Belgium	2/3/2020	4/14/2020	7/10/2020
Brazil	2/25/2020	7/29/2020	11/5/2020
Bulgaria	3/8/2020	4/27/2020	5/30/2020
Canada	1/25/2020	4/22/2020	8/17/2020
Chile	3/3/2020	6/12/2020	11/24/2020
China	12/1/2019	2/14/2020	5/19/2020
Colombia	3/6/2020	8/16/2020	10/4/2020
Croatia	2/25/2020	4/1/2020	6/7/2020
Czech Republic	3/1/2020	3/31/2020	5/13/2020
Denmark	2/27/2020	4/9/2020	7/8/2020
Egypt	2/14/2020	6/16/2020	10/9/2020
Finland	1/29/2020	4/10/2020	7/30/2020
France	1/24/2020	4/18/2020	6/28/2020
Germany	1/27/2020	4/2/2020	6/15/2020
Greece	2/26/2020	4/3/2020	6/3/2020
Guatemala	3/13/2020	7/18/2020	9/5/2020
India	1/30/2020	9/16/2020	2/14/2021
Indonesia	3/2/2020	2/1/2021	5/18/2021
Iran	2/19/2020	4/2/2020	5/3/2020
Israel	2/21/2020	4/5/2020	5/24/2020
Italy	1/30/2020	3/26/2020	6/3/2020
Japan	1/16/2020	4/5/2020	5/27/2020
Kenya	3/13/2020	8/3/2020	9/20/2020
Korea	1/20/2020	3/4/2020	5/6/2020
Macedonia	2/26/2020	4/18/2020	5/8/2020
Malaysia	1/25/2020	4/8/2020	6/6/2020
Mexico	2/28/2020	8/1/2020	9/22/2020
Netherlands	2/27/2020	4/11/2020	7/10/2020
New Zealand	2/28/2020	4/5/2020	8/10/2020
Nigeria	2/27/2020	7/2/2020	10/25/2020
Norway	2/26/2020	3/28/2020	7/22/2020
Oman	2/24/2020	7/15/2020	8/23/2020
Pakistan	2/26/2020	6/19/2020	9/1/2020
Peru	3/6/2020	6/2/2020	7/5/2020
Phillippines	1/30/2020	8/15/2020	1/7/2021
Poland	3/4/2020	11/11/2020	2/8/2021

Supplementary Table 3. Continued

Country	1st reported case*	1st wave peak	Second wave date†
Portugal	3/2/2020	4/11/2020	8/9/2020
Republic of Moldova	3/7/2020	12/11/2020	1/22/2021
Romania	2/26/2020	4/17/2020	6/2/2020
Singapore	1/23/2020	4/26/2020	6/10/2020
Slovakia	3/6/2020	4/20/20	6/4/2020
Spain	1/31/2020	3/31/2020	7/5/2020
Sweden	1/31/2020	6/24/2020	9/2/2020
Switzerland	2/25/2020	3/25/2020	6/8/2020
Taiwan	1/13/2020	3/25/2020	2/17/2021
Thailand	1/13/2020	4/3/2020	11/20/2020
Tunisia	3/2/2020	4/6/2020	6/9/2020
Turkey	3/10/2020	4/16/2020	6/23/2020
United Arab Emirates	1/29/2020	5/22/2020	8/8/2020
United Kingdom	1/31/2020	4/8/2020	7/7/2020
United States	1/20/2020	4/9/2020	7/11/2020
Vietnam	1/23/2020	4/1/2020	7/14/2021

All data of the wave peaks obtained from https://ourworldindata.org/coronavirus a joint project of the University of Oxford and Global Change Data Lab.
*All data of the first reported case by country, defining the onset of the pandemic of the country obtained from Wikipedia[29]; †Definition of the second wave: the number of coronavirus disease 2019 cases must decline >50% from the previous wave's peak and more than double at the next peak. The start date for this occurrence was chosen as the minimum closest to the second wave.

Supplementary Table 4. Cerebral venous thrombosis admissions; overall and monthly volumes first 5 months: 2019 vs. 2020

Variable	Overall volume					Monthly volume*			
	No. of hospital	No.†	No.‡	Change	*P*	No. of hospital	No.†	No.‡	*P*
Overall	162	498	449	−9.8 (−12.7 to −7.5)	0.11	169	0.65±0.12	0.55±0.11	0.03
Primary vs. comprehensive stroke center§									
Primary	39	114	93	−18.4 (−26.5 to −12.4)	0.15	41	0.63±0.18	0.50±0.16	0.19
Comprehensive	123	384	356	−7.3 (−10.3 to −5.1)	0.30	128	0.68±0.18	0.59±0.17	0.07
Center COVID-19 volume‖									
Low	50	79	72	−8.9 (−17.2 to −4.4)	0.57	51	0.62±0.12	0.57±0.09	0.53
Intermediate	49	106	100	−5.7 (−11.8 to −2.6)	0.68	50	0.51±0.19	0.47±0.18	0.38
High	49	236	211	−10.6 (−15.2 to −7.3)	0.24	51	1.15±0.27	1.03±0.26	0.23

Values are presented as percentage (95% confidence interval) or adjusted mean±standard error.
COVID-19, coronavirus disease 2019.
*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent; †Number of admissions during first 5 months of 2019; ‡Number of admissions during the first 5 months of 2020; §Primary vs. Comprehensive, *P*=0.001; ‖Low vs. Intermediate (*P*=0.40), Low vs. High (*P*=0.67), Intermediate vs. High (*P*=0.15).

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Supplementary Table 5. Cerebral venous thrombosis admissions; overall and monthly volumes first 5 months: 2019 vs. 2021

Variable	Overall volume					Monthly volume*			
	No. of hospital	No.†	No.‡	Change	*P*	No. of hospital	No.†	No.‡	*P*
Overall	162	498	635	27.5 (24.2–32.0)	<0.0001	169	0.60±0.14	0.72±0.15	0.09
Primary vs. comprehensive stroke center§									
Primary	39	114	131	14.9 (9.5–22.6)	0.28	41	0.73±0.20	0.80±0.23	0.51
Comprehensive	123	384	504	31.3 (26.8–36.1)	<0.0001	128	0.59±0.21	0.73±0.23	0.12
Center COVID-19 volume‖									
Low	50	79	102	29.1 (20.3–39.9)	0.09	51	0.30±0.15	0.38±0.14	0.18
Intermediate	49	106	152	43.4 (34.4–52.9)	0.004	50	0.41±0.24	0.59±0.24	0.006
High	49	236	304	28.8 (23.4–34.9)	0.004	51	1.20±0.28	1.46±0.35	0.21

Values are presented as percentage (95% confidence interval) or adjusted mean±standard error.
COVID-19, coronavirus disease 2019.
*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent; †Number of admissions during first 5 months of 2019; ‡Number of admissions during the first 5 months of 2021; §Primary vs. Comprehensive (*P*=0.001); ‖Low vs. Intermediate (*P*=0.047), Low vs. High (*P*=0.959), Intermediate vs. High (*P*=0.008).

Supplementary Table 6. Cerebral venous thrombosis admissions; overall and monthly volumes first 5 months: 2020 vs. 2021

Variable	Overall volume					Monthly volume*			
	No. of hospital	No.†	No.‡	Change	*P*	No. of hospital	No.†	No.‡	*P*
Overall	162	449	635	41.4 (37.0–46.0)	<0.0001	169	0.57±0.11	0.80±0.14	0.001
Primary vs. comprehensive stroke center§									
Primary	39	93	131	40.9 (31.4–51.0)	0.01	41	0.54±0.16	0.75±0.21	0.07
Comprehensive	123	356	504	41.6 (36.6–46.8)	<0.0001	128	0.56±0.16	0.80±0.19	0.006
Center COVID-19 volume‖									
Low	50	72	102	41.7 (31.0–53.2)	0.02	51	0.57±0.09	0.70±0.11	0.04
Intermediate	49	100	152	52.0 (42.3–61.5)	0.001	50	0.37±0.18	0.59±0.20	0.002
High	49	211	304	44.1 (37.6–50.8)	<0.0001	51	0.96±0.27	1.34±0.35	0.07

Values are presented as percentage (95% confidence interval) or adjusted mean±standard error.
COVID-19, coronavirus disease 2019.
*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent; †Number of admissions during first 5 months of 2020; ‡Number of admissions during first 5 months of 2021; §Primary vs. Comprehensive (*P*=0.90); ‖Low vs. Intermediate (*P*=0.18), Low vs. High (*P*=0.72), Intermediate vs. High (*P*=0.19).

Supplementary Table 7. Rates of concomitant COVID-19 with CVT admissions

Variable	No. of centers	COVID-19 with CVT	CVT admission	Percentage	95% CI
Overall	163	132	1,738	7.59	6.44–8.93
Asia	43	28	511	5.48	3.82–7.81
North America	35	15	509	2.95	1.80–4.81
Europe	69	61	529	11.53	9.08–14.53
South America	8	15	112	13.39	8.28–20.92
Oceania	3	0	25	0	0.00–13.32
Africa	5	13	52	25.00	15.23–38.21

Time course is from the beginning of the pandemic early 2020, adjusted by each site for country start date (Supplementary Table 2), until May 2021.
COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis; CI, confidence interval.

Supplementary Table 8. The proportion of patients hospitalized with COVID-19 with concomitant diagnosis of CVT

Variable	No. of centers	CVT with COVID-19	COVID-19 admission	Percentage	95% CI
Overall	154	103	292,080	0.04	0.03–0.05
Asia	40	14	47,253	0.03	0.02–0.05
North America	34	14	102,920	0.01	0.01–0.02
Europe	65	50	110,522	0.05	0.04–0.07
South America	7	12	20,912	0.06	0.03–0.10
Oceania	3	0	68	0	0.00–5.35
Africa	5	13	10,405	0.12	0.07–0.21

COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis; CI, confidence interval.

Supplementary Table 9. Mortality as it relates to COVID-19 status during the first year of the COVID-19 pandemic from 120 centers

Variable	Alive	Dead	In-hospital mortality rate (%)	Total
CVT COVID-19 negative	869	41	4.5	910
CVT COVID-19 positive	45	8	15	53
Total CVT admissions	914	49	5.1	963

During the first pandemic year, CVT mortality was higher in patients who were COVID-19 positive compared to COVID-19 negative patients (8/53 [15.0%] vs. 41/910 [4.5%], P=0.004).
COVID-19, coronavirus disease 2019; CVT, cerebral venous thrombosis.

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