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The Hospitalization Rate of Cerebral Venous Sinus Thrombosis before and during COVID-19 Pandemic Era: A Single-Center Retrospective Cohort Study

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Objectives: There are several reports of the association between SARS-CoV-2 infection (COVID-19) and cerebral venous sinus thrombosis (CVST). In this study, we aimed to compare the hospitalization rate of CVST before and during the COVID-19 pandemic (before vaccination program). *Materials and methods:* In this retrospective cohort study, the hospitalization rate of adult CVST patients in Namazi hospital, a tertiary referral center in the south of Iran, was compared in two periods of time. We defined March 2018 to March 2019 as the pre-COVID-19 period and March 2020 to March 2021 as the COVID-19 period. *Results:* 50 and 77 adult CVST patients were hospitalized in the pre-COVID-19 and COVID-19 periods, respectively. The crude CVST hospitalization rate increased from 14.33 in the pre-COVID-19 period to 21.7 per million in the COVID-19 era ($P = 0.021$). However, after age and sex adjustment, the incremental trend in hospitalization rate was not significant (95% CrI: -2.2, 5.14). Patients > 50-year-old were more often hospitalized in the COVID-19 period ($P = 0.042$). SARS-CoV-2 PCR test was done in 49.3% out of all COVID-19 period patients, which were positive in 6.5%. Modified Rankin Scale

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(mRS) score ≥ 3 at three-month follow-up was associated with age ($P = 0.015$) and malignancy ($P = 0.014$) in pre-COVID period; and was associated with age ($P = 0.025$), altered mental status on admission time ($P < 0.001$), malignancy ($P = 0.041$) and COVID-19 infection ($P = 0.008$) in COVID-19 period.

Conclusion: Since there was a more dismal outcome in COVID-19 associated CVST, a high index of suspicion for CVST among COVID-19 positive is recommended.

Key Words: Sinus thrombosis—Stroke—COVID-19—SARS-CoV-2—Prognosis—Hospitalization rate

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Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon though potentially fatal cerebrovascular disease which mainly affects the younger and female population.^{1,2} However, timely diagnosis and treatment may lead to better outcomes.^{3,4} The CVST incidence varies between 5 and 20 per million annually.^{5–8} The CVST is more frequent in the Middle East and southern Asia than in Western countries.^{1,9} The annual hospitalization rate of CVST was reported as 12.3 and 13.49 per million in Iran.^{10,11}

Since the emergence of the Coronavirus Disease 2019 (COVID-19) pandemic, there have been rising concerns about neurological complications associated with COVID-19, particularly thrombotic events.¹² Some studies have demonstrated the predominance of venous thromboembolic manifestations, especially in the critically ill groups.^{13,14} There are growing numbers of case reports and case series investigating the association between CSVT and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.^{15,16}

The current study was designed to compare the hospitalization rate of CVST before and during the COVID-19 pandemic era in a referral center in Iran. We also assessed the changes in the rate of mortality, disability, and epidemiological shifts in aging and sex distribution.

Materials and methods

This retrospective cohort study was conducted in the Namazi hospital, a major referral center for stroke in Shiraz with a large catchment area in the Fars province (southern Iran). The study periods were defined as a) pre-COVID period [21st March 2018 to 20th March 2019] and b) COVID-19 period [20th March 2020 to 20th March 2021]. Iran reported its first confirmed case of COVID-19 on 19th February 2020.¹⁷ The National COVID-19 vaccination program was started after the recruitment time.¹⁷ Accordingly, no recruited patient was vaccinated. As all official medical and demographic reports are presented in the Iranian calendar, which starts on 21st March, the above-mentioned dates were selected for the study periods.¹⁸

According to the Statistical Center of Iran, the estimated > 20-year-old population of Fars province in the first and second period was 3,487,000 and 3,547,000 people,

respectively, based on the National Population and Housing Census results in the year 2016.¹⁹ Namazi hospital covers all CVST patients from the metropolitan area of Shiraz and severe CVST patients from other parts of Fars province. The referral system from the catchment area had no change between the pre-COVID period and the COVID period. Urban and rural areas are defined according to the Statistical Center of Iran.¹⁹

Definitions

All patients with age > 20-year-old with the definite final diagnosis of CVST were included in our study. The diagnosis criteria of CVST was based on the presence of relevant clinical symptoms and radiological assessments of the brain (Computed Tomography -CT-, CT venography, Magnetic resonance imaging -MRI- or MR venography).²⁰ Patients with incomplete medical records as well as patients with indefinite diagnosis were excluded.

We entered all data from patients diagnosed with CVST from the time of admission into a newly organized registry system designed by the engineering team of the Neurology Research Center of Shiraz University of Medical Sciences (Iran ministry of health registry code: 9001013381). All neurologists who work in our center were affiliated to this registry and actively enrolled CVT patients. To ensure full entry of patients in the registry system, using the international classification of diseases 10th version (ICD-10), we searched all medical records with *primary* ICD-10 diagnostic codes of G08 for "Intracranial and intraspinal phlebitis and thrombophlebitis", O87.3 for "Cerebral venous thrombosis in the puerperium", I63.6 for "Cerebral infarction due to cerebral venous thrombosis, nonpyogenic", I67.6 for "Non-pyogenic thrombosis of the intracranial venous system" and I61.9 for "Non-traumatic intracerebral hemorrhage". Thereafter, miscoded patients were excluded by a vascular neurologist.

COVID-19 attributed investigations were done for patients if *any* clinical relevance was found. COVID-19 is considered in patients with positive reverse transcriptase-polymerase chain reaction (RT-PCR) from the oro- or naso-pharynx.²¹ Patients who developed COVID-19 infection as a nosocomial infection was excluded.

Disability or death at the time of discharge and three-month follow-up was assessed according to the modified

Rankin Scale (mRS) score. Poor outcome is defined as mRS ≥ 3 at discharge and three-month after the index event.

Statistical analysis

Analysis was performed on the data using IBM SPSS Statistics for Windows, Version 16.0. Armonk, NY: IBM Corp. The P -value < 0.05 is considered significant in all analyses.

The crude hospitalization rate per 1,000,000 population in the two periods was the dependent variable. The quantitative variables are shown using mean \pm standard deviation (SD) or median with interquartile range (IQR) according to the distribution pattern. The qualitative variables are reported using numbers with percentages (%). A Chi-Square test was used to compare the hospitalization rate change between pre-covid-19 and COVID-19 periods. Beside, independent variables (e.g., predisposing risk factors and main demographic variables) were compared using Chi-Square tests. Due to the non-normally distributed pattern of our data, we applied the Mann-Whitney test to compare the age of participants between pre-COVID19 and COVID-19 periods. In addition, using Cox Proportional Hazards regression analysis, we compared the adjusted Hazard ratio (aHR) of mortality between mentioned periods. To evaluate the trend of crude hospitalization rate of CVST, aggregated monthly hospitalization of CVST was used.

Bayesian interrupted time series was used to examine the change of hospitalization rate across the study period. The BSTS package was used to perform time series analysis in the R 4.1 environment. The final time series model was fitted with adjusting the effects of age and male to female ratio variables. The 95% Credible Intervals (CrI) were used to report the Bayesian time series model results.

Study protocol approval

The institutional review board and the Ethics Committee of Shiraz University of Medical Sciences (SUMS) approved the study protocol (IR.SUMS.REC.1399.098). This study follows the ethical standards of the institutional and national research committee and with the Helsinki Declaration or comparable ethical standards.²² Data

can be shared with other centers upon the approval of the Ethics Committee.

Results

Crude hospitalization rate

50 and 77 adult CVST cases were registered in the pre-COVID and COVID-19 periods, respectively. Therefore, the estimated crude hospitalization rate of CVST increased from 14.33 (95% CI: 10.35 to 18.3) per million in the pre-COVID period to 21.7 (95% CI: 16.85 to 26.54) per million per year during the COVID-19 period (95% CI for proportions: 0.8 to 13.9; $P = 0.021$). Excluding COVID-19 associated CVST patients- 5 patients- from the second period shows that the non-COVID-19 associated CVST hospitalization rate increased from 14.33 (95% CI: 10.35 to 18.3) in the pre-COVID period to 20.29 (95% CI: 16.85 to 26.54) per million which was not significantly different (95% CI for proportions: -0.46 to 12.4; $P = 0.058$) (Table 1).

During the COVID-19 pandemic period, the female-to-male ratio changed from 3:1 to 2:1, although it was not significant ($P = 0.305$) compared to the pre-COVID period. In addition, the median age of CVST patients increased from 40.5 [29, 45.25] to 41 [35.5, 55.5] during the study period ($P = 0.037$) and the proportion of the patients > 50 -year-old, increased in the COVID-19 pandemic era ($P = 0.042$). The most common presentation was a headache in both intervals, including 88 and 81.8 % of patients in the first and second periods. Other symptoms were visual symptoms (34 % and 31.2%), seizure (40% and 33.8%), motor involvement (30% and 37.7%), paresthesia (14% and 9.1%), slurred speech (30 % and 19.5%) and cranial nerve palsy (14% and 7.8%). Table 2 represents the comparison of clinical characteristics of CVST patients between the mentioned periods.

Predisposing risk factors

Sex-specific risk factors-pregnancy, puerperium, and oral contraceptives- comprised the largest etiological group representing 56 % of all cases (73.7% of female patients) in the pre-COVID period and 42.9% (61.5% of female patients) in the COVID-19 period had at least one of these risk factors. There was a high proportion of infectious causes in the COVID-19 period; however, this was not statistically significant (8% vs. 19.5% in period 2, $P = 0.076$). SARS-CoV-2 PCR test was done in 38 patients

Table 1. Crude cerebral venous sinus thrombosis hospitalization rate per million before and during COVID-19 pandemic.

	Pre-COVID period	COVID-19 period	P -value
General population	14.33	21.70	0.021*
Male population	6.82	14.00	0.037*
Female population	21.99	29.51	0.167
< 50 -year-old population	17.84	21.44	0.362
≥ 50 -year-old population	5.18	22.30	0.001*

Table 2. Demographic criteria and clinical characteristics of CVST patients.

		Pre-COVID period N = 50	COVID-19 period N = 77	P-value
Age (median, IQR)		40.5(29,45.25)	41(35.5,55.5)	0.037**
Sex	Male	12 (24%)	25 (32.5%)	0.305
	Female	38 (76%)	52 (67.5%)	
Residence	Rural	10 (20%)	6 (7.8%)	0.043**
	Urban	40 (80%)	71 (92.2%)	
Previous CVST		1 (2%)	0	0.394
Previous DVT or PTE		3 (6%)	5 (6.5%)	1.000
Family history of CVST		2 (4%)	2 (2.6%)	0.646
Family history of DVT or PTE		2 (4%)	4 (5.2%)	1.000
Presentation syndrome	Focal neurological deficit	12 (24.5%)	20 (26%)	0.920
	Increased ICP syndrome	9 (18.4%)	10 (13%)	
	Isolated headache	13 (26.5%)	19 (24.7%)	
	Encephalopathy syndrome	8 (16.3%)	15 (19.5%)	
	Unspecified	7 (14.3%)	13 (16.9%)	
Mode of onset	Acute	36 (72%)	50 (65.8%)	0.214
	Subacute	13 (26%)	19 (25%)	
	Chronic	1 (2%)	7 (9.2%)	
Sinus involvement	Mainly Superficial	40 (80%)	63 (81.8%)	0.798
	Mainly Deep	10 (20%)	14 (18.2%)	
Intracranial hemorrhage		22 (44%)	31 (40.3%)	0.676
Mental status disturbance on admission		16 (32%)	32 (41.6%)	0.278
Comatose on admission (GCS<9)		0	3 (3.9%)	0.278
Discharged anticoagulants ^a	Warfarin	39 (86.7%)	43 (66.2%)	0.012**
	DOACs	6 (13.3%)	12 (18.5%)	
	Enoxaparin	0	10 (15.4%)	
Mortality rate	< 28 days	3 (6%)	11 (14.3%)	0.215
	>28 days	2 (4%)	1 (1.3%)	0.561
Ramadan-month admission		5 (10%)	6 (7.8%)	0.751
Outcome at discharge ^b	Favorable	35 (70%)	43 (55.8%)	0.109
	Poor	15 (30%)	34 (44.2%)	
Outcome at 3-month follow-up ^{b, c}	Favorable	41 (87.2%)	58 (77.3%)	0.174
	Poor	6 (12.8%)	17 (22.7%)	

**All data is shown as N (%). DOACs, direct oral anticoagulants; DVT, Deep Vein Thrombosis, PTE, Pulmonary Thromboembolism. a:45 and 65 patients were discharged in pre-COVID and COVID-19 periods, respectively. b: Favorable outcome is defined as MRS 0-2 and poor outcome is defined as MRS 3-6. c: 3-month follow-up MRS score was available in 47 and 75 patients in pre-COVID and COVID-19 periods.

(49.3%) out of all COVID-19 period patients who were positive in 5 patients (6.5%). Overall, there was no difference regarding the predisposing factors between pre-COVID and COVID-19 periods.

Temporal trend of hospitalization rate of CVST

The monthly crude hospitalization rate of CVST in the two periods is illustrated in Fig. 1. During the COVID-19 period, the hospitalization rate of CVST had an average value of 1.67 patients per month. Although, it was 1.07 [95% CI: 0.77, 1.37] at pre-COVID-19 period. The estimated rising in cumulative hospitalization rate was +56% [95%CI: +28%, +84%]. A significant increase in hospitalization rate was observed by 21.65 ($P = 0.002$). However, without COVID-19 we expected a value of about 13.85 [95% CI: 9.98, 17.82]. Including confounder variables to the Bayesian interrupted time series model, a stable trend of hospitalization rate was observed (Posterior Beta of time*period interaction=0.05; 95% CrI: -0.28, 0.17). In addition, the hospitalization rate raised by 1.4 times in the COVID-19 period compared to the pre-covid-19 period, but it was insignificant (95% CrI: -2.2, 5.14). The estimated expected and observed trend of hospitalization rate from the time series model is shown in supplemental Fig. 1.

Survival analysis

The 28-day crude mortality rate of CVST was 6% in the pre-COVID period and 14.3% in the COVID-19 period, a non-statistically significant difference ($P = 0.145$).

Excluding COVID-19 associated CVST patients, the 28-day mortality rate was 11.1% in the COVID-19 period. Moreover, COVID-19 associated CVST patients had higher 28-day mortality than the other patients in the COVID-19 period (60% vs. 11.1%, $P = 0.019$). This higher non-significant mortality rate in COVID-19 period could be due to secondary infections.²³ While in the pre-COVID period, head and neck infections including mastoiditis and sinusitis were the most common predisposing infections (8%), COVID 19 (6.5%), mucormycosis (3.9%), meningitis, and sepsis (2.6%) struck the patients in the COVID-19 period, as well as head and neck infections (6.5%).

The Cox proportional analysis after adjusting for age and sex did not show a statistically significant difference in adjusted HR of mortality during the COVID-19 pandemic [aHR: 1.83, 95%CI: (0.51, 6.62)].

Among the discharged patients, 42 patients in the pre-COVID period and 63 in the COVID-19 period were recruited in three-month follow-up either by face-to-face interview or telephone interview. 3-month mRS scores of patients are illustrated in Fig. 2.

Poor outcome at three month-follow-up in the pre-COVID period was associated with age ($P = 0.015$) and malignancy ($P = 0.014$). In contrast, in the COVID-19 period, it was associated with higher age ($P = 0.025$), altered mental status on admission time (P -value <0.001), malignancy ($P = 0.041$), and COVID-19 infection ($P = 0.008$). However, it was not associated with gender, intracranial hemorrhage, thrombosis of the deep venous

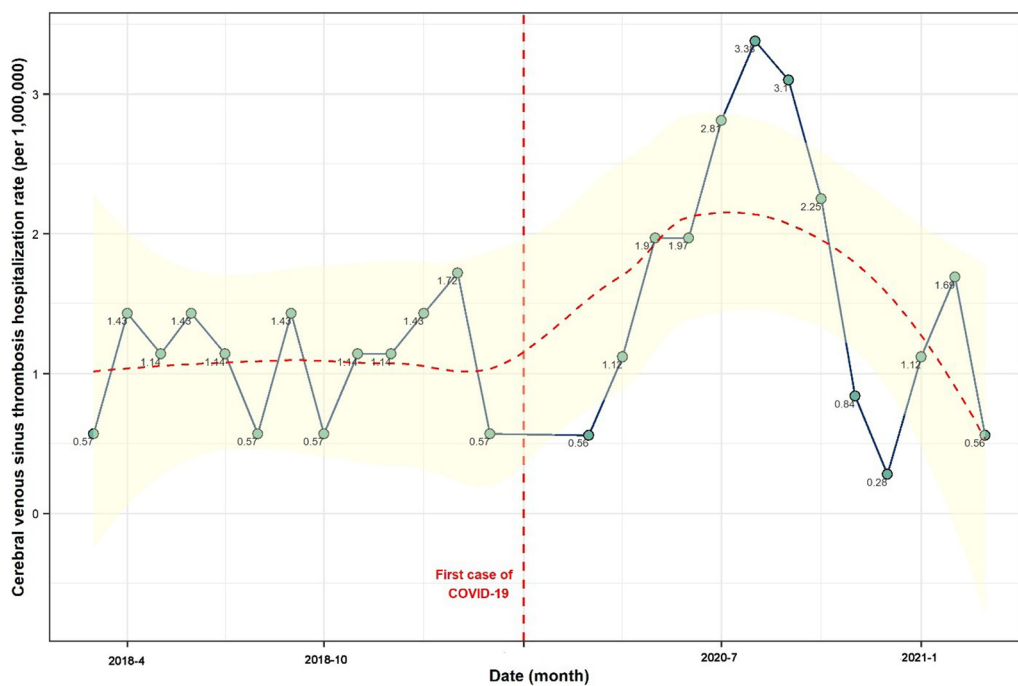


Fig. 1. Crude monthly CVST hospitalization rate per 1,000,000 across pre-COVID-19 and COVID-19 periods.

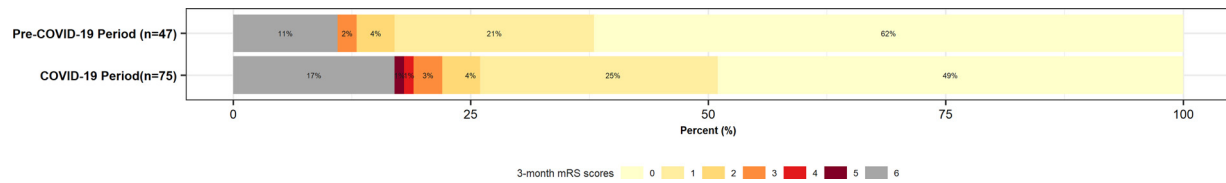


Fig. 2. Three-month mRS score in pre-COVID and COVID periods.

system, and comatose status on admission in none of the two periods.

Discussion

In our study, the crude hospitalization rate of CVST patients older than 20 increased significantly from the pre-COVID period to the COVID-19 period. Although, after age and sex adjustment, the incremental trend was not significant. During the COVID-19 era, the median age of the CVST patients increased as compared to the pre-COVID period. No predisposing risk factor was different between mentioned periods. COVID-19 associated CVST patients had higher 28-day mortality than the other patients in the COVID-19 period.

There have been several case series and case reports of association of CVST and COVID-19 infection.^{15,24–28} In a systematic review, CVST frequency was 0.08% among hospitalized COVID-19 patients.²⁹ A retrospective cohort study using electronic health records of 537,913 patients with COVID-19 infection demonstrated the incidence of CVST in two weeks after a COVID-19 diagnosis was 42.8 per million people, which was significantly higher than in a matched cohort of people who received an mRNA vaccine and patients with influenza.³⁰

However, asymptomatic COVID-19 infection might trigger thrombosis, particularly in patients with predisposing risk factors.³¹ About 16% of patients with SARS-CoV-2 infection might be asymptomatic.³² If these patients refer to the hospital more than 14 days after SARS-CoV-2 infection, there is a high probability for nasopharyngeal COVID-19 RT-PCR to be negative.³³ Therefore, the underestimation of COVID-19 cases among CVST patients is possible in our study.

We found that the older population was more affected in the COVID-19 than in the pre-COVID period. This is contrary to previous pre-pandemic reports illustrating younger patients' predominance.^{6,34} Similar to the results of the current study, a multicenter study indicated COVID-19 related CVST was more prevalent among the elderly in comparison with previously reported CVST cases.³⁵ In the retrospective cohort study on COVID-19 hospitalized patients, a male preponderance and average age of 49 years were reported.³⁶

The 28-day mortality rate and 3-month poor outcome -mRS ≥ 3 - had no significant change from pre-COVID to COVID-19 period. Although, a higher 28-day mortality rate was seen among COVID-19 patients. Our results are

consistent with the other studies representing high in-hospital mortality in COVID-19 associated CVST patients.^{16,29,37} However, this finding was not universal. In a multinational case series, poor outcome and in-hospital mortality among COVID-19 associated CVST patients did not differ significantly compared to control CVST patients without COVID-19 infection.¹⁵

This study has some limitations. It should be stressed that the single-centered design and small sample size of the current study decrease our findings' generalizability. To solve this issue, this study should carry on in a large-scale multi-center study.²⁵ The small number of deaths also prevented multivariate analysis for the detection of the determinants of mortality. Moreover, only clinically suspected CVST patients had been tested for COVID-19 infection during the pandemic, and asymptomatic COVID-19 patients might be missed in this study. As a drawback, the number of patients with indirect evidence of recent SARS-CoV-2 infection such as increased D dimer but negative COVID-19 RT-PCR was not determined in the current study. In addition, in patients with severe COVID infection and decreased level of consciousness, CVT might have been overlooked. In addition, mild cases of CVST might not have been referred to the hospital due to COVID-19 phobia, similar to other mild cerebrovascular diseases.³⁸ Our center covers all mild to severe CVST patients from the metropolitan area of Shiraz and severe CVST patients from other parts of Fars province. Therefore, mild cases of other parts of this province might not be included in our study. However, the referral and admission system of our center did not change between 2018 and 2020. Nevertheless, we believe our registry system, which included all hospitalized CVST patients in our setting, was our study's strength.

Conclusion

In conclusion, we observed a significant increase in crude CVST hospitalization rate but not in sex and age-adjusted CVST hospitalization rate. In line with several previous studies, we found higher mortality and worse three-month disability in COVID-19 associated CVST. This highlights the importance of a high index of suspicion for this diagnosis among COVID-19 positive patients to allow early diagnosis and treatment.

As many CVST patients present with isolated headache and headache can also be a presentation of SARS-CoV-2 infection, progressive headache even in the absence of

neurologic deficits should be evaluated vigilantly in this regard.²⁷ In addition, as the elderly became more affected during the pandemic period, we strongly recommend considering CVST as an important differential diagnosis in this population. To re-examine our findings, similar studies should be carried out on a large-scale multi-center basis.

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Ethical standards

This study was approved by the ethics committee and institutional review board of Shiraz University of Medical Sciences (IR.SUMS.REC.1399.098).

Informed consent

All participants gave their informed consent prior to their inclusion in the study.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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