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.

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Letter to the Editor

Impact of cerebral venous sinus thrombosis associated with COVID-19

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1. Introduction

Thromboembolism is one of the major complications of coronavirus disease 19 (COVID-19) [1]. Both arterial and venous thromboembolism involving various organs from COVID-19 related coagulopathy have been reported. While arterial ischemic strokes are common, cerebral venous sinus thrombosis (CVT) associated with COVID-19 has been increasingly recognized [2,3]. The true incidence of CVT in COVID-19 patients remains unknown. Various mechanisms of thromboembolism include elevated factor VIII, fibrinogen, D-dimer, prothrombotic microparticles like antiphospholipid antibodies, and inflammatory markers like C-reactive protein and interleukin-6 [4]. In this report, we aimed to determine the rates of CVT and its impact on outcomes in patients with COVID-19.

2. Methods

De-identified patient information was extracted on March 1st, 2021 using the TriNetX COVID-19 Research Network platform (www.trinetx.com) [5]. TriNetX is a global health collaborative clinical research platform that collects real-time electronic medical records data from a network of health care organizations (HCOs), typically academic medical centers and their affiliates, across the world. On March 24th, 2020, TriNetX updated its real world platform to incorporate specific COVID-19 terminology and to support COVID-19 related research, thus creating one of the largest COVID-19 datasets. This included updated diagnosis, World Health Organization (WHO), and Centers for Disease Control (CDC) specific coding guidelines. While the TriNetX platform does not provide individual patient data review or data downloads, it allows analysis in the form of queries accessing its real-time features.

This study was exempt by our institutional IRB as it consisted of global deidentified patient data. Patients of $\geq$ 18 years of age suffering from CVT with or without COVID-19, irrespective of their need for hospitalization, were identified. The baseline characteristics and comorbidities were compared between the two groups using the statistical function performed through TriNetX analytics statistical function. Any group with less than 10 observations was reported as $\leq$ 10 by the software to protect patient identification.

The prevalence of CVT and its outcomes in the setting of COVID-19 infected versus uninfected population were compared using Chi-square analysis if all the data points had values greater than or equal to five. We used the two-sided Fisher's Exact test if any of the data points contained a value smaller than five. We used STATA 16.0 software for analysis.

3. Results

From this dataset, we identified 667,551 COVID-19 patients of which 42 had CVT, and 65,796,480 non COVID-19 patients of which 1022 had CVT (0.0001 vs 0.000002, OR = 40.99 [95% CI = 30.11 - 55.81], $p <$ 0.00001). Among the 42 COVID-19 patients with CVT, 24 (57.1%) were females and 28 (66.6%) were Caucasians. The baseline characteristics and comorbidities of patients with CVT among COVID-19 positive and COVID-19 negative patients are described in Table 1. A significantly higher prevalence of hypertension ($p = 0.0278$) and diabetes mellitus ($p = 0.0107$) was observed in patients suffering from CVT with COVID-19 compared to the non COVID-19 cohort. A significantly higher mortality rate was observed in patients suffering from CVT with COVID-19 compared to the non COVID-19 cohort (11.9% vs 2.8%, OR = 4.627 [95% CI = 1.320–13.032], $p = 0.0011$). There were no significant differences between both groups in terms of the need for intubation (2.4% vs 2.3%, OR = 1.014 [95% CI = 0.024 - 6.544], $p = 1.0$) and the admission to critical care services (7.1% vs 9.1%, OR = 0.768 [95% CI = 0.149 - 2.492], p = 1.0).

4. Discussion

CVT is a well-known complication following COVID-19 coagulopathy. Although arterial events are common in COVID-19 patients, CVT must be considered in the evaluation of patients with persistent headaches, focal neurological deficits, and encephalopathy once ischemic strokes are ruled out. The frequency of CVT in COVID-19 patients was less than 0.0001%, which is lesser than the frequency of 0.08% reported in a recent systematic review [3]. However, the odds of developing CVT among COVID-19 patients in our study were 41 times higher than among non-COVID-19 patients which comes in line with the known increased hypercoagulable state associated with patients infected with the COVID-19 virus. We identified a higher prevalence of hypertension and diabetes mellitus among patients suffering from CVT with COVID-19. These are known risk factors of severe disease and mortality in COVID-19 infected patients [6]. Various studies have reported known predisposing factors of CVT in 23% to 31% of COVID-19 patients [3,7]. The mortality rate in

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Table 1
Characteristics of CVT* in patients with and without COVID-19**.

Variable	COVID With CVT 42 of 667,551	Non COVID with CVT 1022 of 65,796,480	*p*-value
Age (years)	51 ± 18.1	50.1 ± 18.9	0.756
Gender (females)	24 (57.1%)	638 (62.4%)	0.488
Ethnicity			
Caucasian	28 (66.6%)	644 (63.0%)	0.6305
African American	≤ 10 (23.8%)	140 (13.7%)	NA
Hispanic	≤ 10(23.8%)	75 (7.34%)	NA
Asian	≤ 10(23.8%)	25 (2.45%)	NA
American Indian	≤ 10(23.8%)	10 (0.98%)	NA
Hypertension	21 (50%)	343 (33.56%)	0.0278
Diabetes mellitus	12 (28.57%)	146 (14.29%)	0.0107
Atrial fibrillation	≤ 10 (23.81%)	64 (6.26%)	NA
Congestive heart failure	≤ 10 (23.81%)	69 (6.751%)	NA
Ischemic heart disease	≤ 10 (23.81%)	98 (9.59%)	NA
Chronic kidney disease	≤10 (23.81%)	82 (8.02%)	NA
Nicotine dependence	≤10 (23.81%)	136 (13.31%)	NA
Overweight	11 (26.19%)	198 (19.37%)	0.276

≤ Range varies from 1 to 10 patients; NA – Not applicable.

patients suffering CVT is higher among COVID-19 patients than the general population [3]. However, this rate (11.9%) was lower than the mortality rates in a recent systematic review and meta-analysis (40–45%) [3,8]. Nonetheless, this meta-analysis was based on case reports and case series and did not correlate it with the mortality rates of uninfected patients suffering from CVT. Our study showed that the mortality from CVT is 4.6 times higher in COVID-19 patients than in the general population. This is possibly due to a more aggressive hypercoagulable state in patients infected with COVID-19 virus.

Our study has several limitations, which include the retrospective nature of the study. In addition, we did not adjust for the severity of CVT, COVID-19 infection, or the cause of death. Our data was limited to that of the hospitals from where patients were admitted. Our data did not include neurological outcome, information of pharmacological prophylaxis, the status of immobility, or other risk factors of coagulopathy.

However, major advantages of our study include that we obtained the data from a single large dataset of COVID-19 patients as opposed to various case series or meta-analyses. Large population-based registries will highlight the true impact of CVT in COVID-19 patients. Another strength of our study is that it provides comparative data on the risk of CVT and its mortality in COVID-19 patients compared to the non-COVID-19 patients.

Contributions

All authors have made substantial contributions to the data collection, drafting of the manuscript, and have accepted the contents prior to submission.

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Conflicts of interest

All authors have no conflict of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.117448.

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