EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 7
434-440
Year: 2022

CEREBRAL VENOUS SINUS THROMBOSIS (CVST) FOLLOWING COVID-19 VACCINATION: A SYSTEMATIC REVIEW OF RECENT EVIDENCE

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Article Received on 19/05/2022 **Article Revised on 09/06/2022** **Article Accepted on 29/06/2022**

ABSTRACT

Background: With 4.45 billion people vaccinated against COVID-19 so far, it is imperative to note the correlation of COVID-19 Vaccination with a rare neurological disorder – cerebral venous sinus thrombosis (CVST) in current literature. This study aims to synthesize the clinical, managerial, and death outcomes of CVST post-COVID-19 vaccination. **Methods:** As per the PRISMA Statement 2020 guidelines, case series and cohorts that comprised of confirmed CVST patients were included. A systematic search across PubMed, Cochrane Central, and EMBASE were conducted through March 10, 2022, with keywords including COVID-19, SARS-CoV-2, CVST, Cerebral, Venous, Sinus, Thrombosis, Thrombotic, TTS, VITT. The findings were tabulated, quantified, and subsequently presented. EndNote X9 was used to store the bibliographic entries and SPSS was utilized for statistical analysis. Cohen's Coefficient of Agreement was also computed for inter-reviewer agreement. **Results:** In total, 9 studies were included in the review totaling 8,131,391 participants. There was a total of 4,397,516 females (54.1%). The mean age was 47.4 years. The mean days between vaccination and presentation was 8 for all included studies. Among CVST patients (N=777), 197 of them did not survive (25.4%). The inter-reliability score was strong (0.83). **Conclusion:** While COVID-19 vaccine-caused CVST is prone to any age group and gender, this study finds that women in the age group of 30-49 are at a higher risk. Both mRNA and adenoviral vaccines may lead to CVST. While the disease has a high mortality, a timely diagnosis may protect from adverse outcomes among the patient group. It is evident that a high degree of caution is required with at-risk groups by healthcare providers, but excessive concern among the general public may be unwarranted. While this study sets the groundwork to establish the correlation between CVST and mortality, further studies are required to truly compute the causality between the COVID-19 vaccine and CVST.

KEYWORDS: COVID-19; COVID-19 vaccine; CVST; cerebral venous sinus thrombosis; vaccine.

INTRODUCTION

As of 10 March 2022, more than 10.9 billion doses of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines have been administered worldwide.[1] Thus far, 4.45 billion people have been fully vaccinated.[1]

Most of the developing/developed vaccines against COVID-19 are focused on the coronavirus spike protein (S protein) and its many variants, the primary antigens of COVID-19 infection; the S protein triggers T-cell and B-cell immune responses.[2] However, other proteins of the coronavirus are also being utilized for vaccine development such as the nucleocapsid. mRNA vaccine comprises vaccines such as Moderna and Pfizer-BioNTech, which are developed using RNA to stimulate an immune response. When these vaccines are introduced into the human tissue, they contain either the messenger RNA or self-replicating RNA which causes cells to express the SARS-CoV-2 spike protein. RNA vaccines often use nucleoside-modified messenger RNA. On the orther hand, adenovirus vector vaccines are non-replicating viral vector vaccines that use an adenovirus shell containing DNA that encodes the SARS-CoV-2 protein. Since these vaccines are non-replicating; they do not produce new virus particles, but the antigen that elicits the systemic immune response. These vaccines include the Oxford-AstraZeneca COVID-19 vaccine, Janssen COVID-19 vaccine, Sputnik V, and Convidecia. Third, inactivated virus vaccines consist of viral particles that are previously cultured and killed using formaldehyde or heat to lose disease-producing capacity, while still promoting an immune response. Examples of these include the Chinese CoronaVac, Sinopharm, and WIBP; the Russian CoviVac, and the Indian Covaxin, in addition to other types. Other vaccines types, beyond the scope of this paper, include those in clinical trials such as virus-like particle vaccines, conjugate vaccines, vesicular stomatitis virus vaccines, and DNA plasmid vaccines.[2,3]

Rare neurological adverse events such as Guillain-Barre syndrome have been reported in literature following SARS-CoV-2 vaccination.[4] On rare occasions, an immune thrombocytopenic disorder associated with cerebral venous sinus thrombosis (CVST) has been reported following vaccines such as the adenovirus-based ChAdOx1 and Ad26.COV2.S.[5] Vascular thrombotic conditions are particularly at high risk among young women that target the cerebral venous sinus vessels.[6,7] Blood clots are also associated with thrombocytopenia, in addition to the novel vaccine-induced immune thrombocytopenic thrombocytopenia (VITT) syndrome that was established in February 2021.[8] Among the general population, CVST is considered to be an excessively rare disease affecting only 1 in 1,000,000 people and 1 in 5000-15,000 hospitalized patients with comorbidities.[9]

With multiple reports of CVST post-SARS-CoV-2 vaccination in literature, the warning of this rare neurological disorder occurring within 15 days after acquiring the first vaccine shot warrants exploration. This study aims to synthesize the clinical, managerial, and mortality outcomes of CVST after the coronavirus disease 19 (COVID-19) vaccination.

METHODS

In accordance with the PRISMA Statement 2020 guidelines, cohorts and case series that included confirmed CVST cases in COVID-19 vaccinated patients as per the WHO criteria were included.[10] The studies reported on the risk factors, clinical outcomes, treatments, and prognostic outcomes of patients that acquired CVST due to any COVID-19 vaccination. The data were systematically entered onto a pre-planned spreadsheet as (Author and Year, Country, Study Type, Patient Count, Gender, Mean Age, Vaccine Type, Site of thrombosis/Concomitant conditions, Risk Factors, Days after vaccination (mean), Management, and Mortality). The patients included had no age or gender limitation and were only excluded if they did not have confirmed CVST. For this review, case reports were excluded. No restrictions were laced on the days' post-vaccination and presentation. The patients typically had any severity of disease (mild, moderate, or severe) as per the NIH classification.

Three databases were searched including PubMed, Cochrane Central, and EMBASE from December 2018 until March 10, 2022. Manual searches of the reference lists were conducted in an effort to not omit any studies (umbrella methodology). The search terms across the databases and registers were a combination of the following: COVID-19, SARS-CoV-2, CVST, Cerebral, Venous, Sinus, Thrombosis, Thrombotic, TTS, VITT. No language restrictions were implemented, and in the case of non-English studies, google translate was used.

The titles and abstracts of all screened studies from the databases and additional resources were screened by all authors. Once the studies were screened and shortlisted, all authors conducted full-text reviews of the studies. Cohen's Coefficient of Agreement was calculated to compute the inter-reviewer agreement. All the identified studies were entered into EndNote X9 (Clarivate Analytics) for reference management. SPSS V 20 was utilized for statistical analysis. The methodology was both quantitative and analytical with means and standard deviation computed for numerical values. Other findings were pooled together and presented in the results.

RESULTS

The PRISMA flowchart is presented in Figure 1. In total 249 studies were identified from databases and registers of which 32 were duplicates. The total number of screened studies was 217, all of which were sought for retrieval. During the eligibility stage, 40 full-text studies were retrieved of which 31 were excluded for missing data or meeting the exclusion criteria. Finally, 9 studies were included in this review (Figure 1). Kappa's inter-rater reliability score was computed to be 0.83, meaning that there was a strong level of agreement.

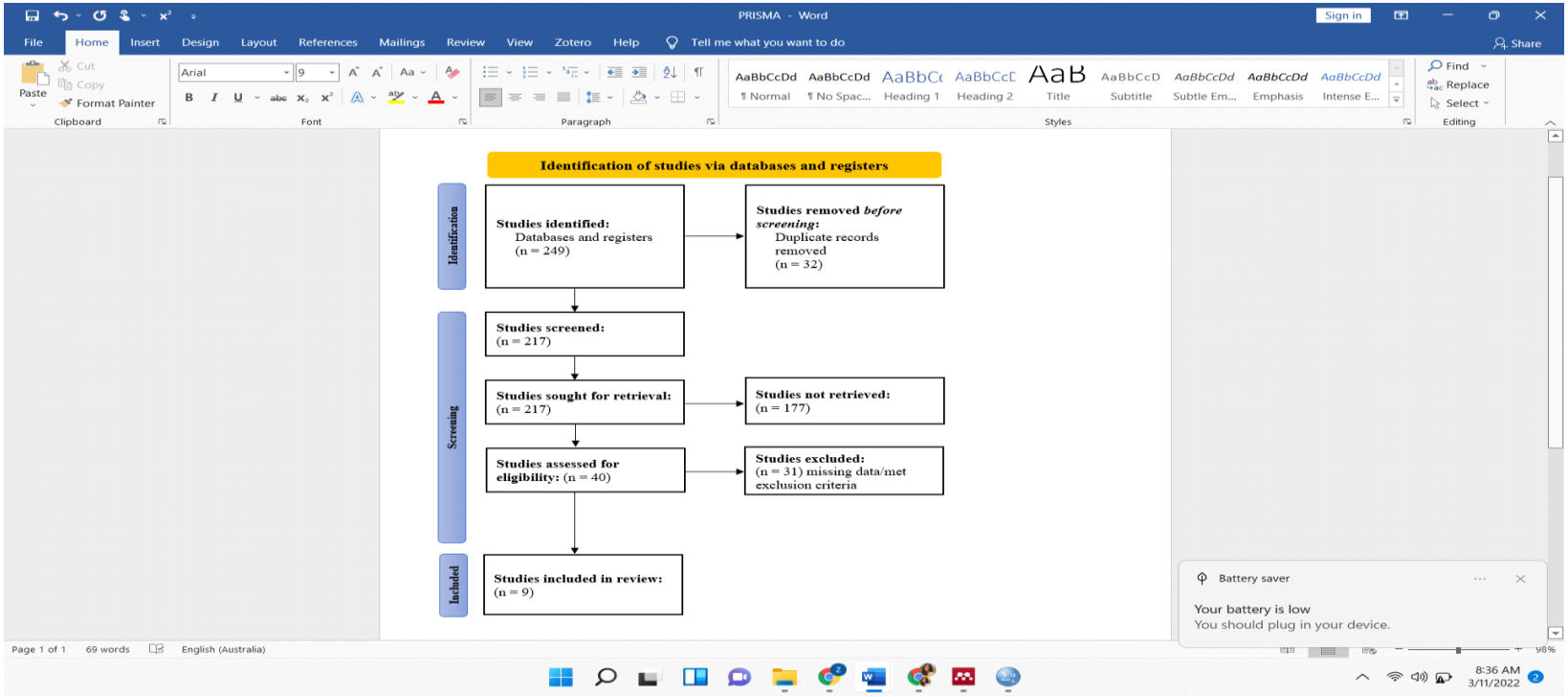

Figure 1: PRISMA flowchart showcasing the study selection process.

Table 1: Characteristics of Studies Included. COPD=Chronic Obstructive Pulmonary Disease; DLP= Dyslipidemia; DM=Diabetes Mellitus; DVT=Deep Vein Thrombosis; HF=Heart Failure; HTN=Hypertension; ITP=Immune Thrombocytopenia; IV=Intravenous; IVIG=Intravenous Immunoglobulins; LMWH=Low Molecular Weight Heparin; NR=Not Reported; RBC=Red Blood Cell; TIA=Transient Ischemic Attack; VTE=Venous Thromboembolism.

Author and Year	Country	Study Type	Patient Count (n)	Gender	Mean Age (years)	Vaccine Type	Site of thrombosis /Concomitant conditions	Risk Factors	Days after vaccination (mean)	Management	Mortality
Welsh et al., 2021[11]	USA	Case Series	28	15 Females, 11 Males, 2 Unkown	48.5	Pfizer-BioNTech, Moderna	Scleral hemorrhage, intracranial hemorrhage, thrombocytopenia, myocardial infarction	3=ITP, 1=Crohn's disease, 1=Type 2 diabetes, 1=Hashimoto's thyroiditis, 1=Psoriasis	7	Prednisone, platelet and RBC transfusion, eltrombopag, dexamethasone, cyclosporine, rituximab, IVIG, emergent craniectomy, splenectomy, Unspecified brain surgery,	2/28 (7.1%)
Scully et al., 2021[12]	UK	Cohort	23	14 Females, 9 Males	44.2	ChAdOx1 nCoV-19	Cerebral venous thrombosis, portal vein thrombosis, ischemic bowel with infarction, intracerebral	No previous prothrombotic medical conditions	12.4	Administration of a non-heparin anticoagulant agent and intravenous immunoglobulin.	16/23 (69.6%)

							hemorrhage, portal vein thrombosis, pulmonary embolism, Subarachnoid hemorrhage, DVT, Pulmonary Embolism, cerebral venous thrombosis, intracerebral hemorrhage				
Andreas et al., 2021[13]	Germany & Austria	Case Series	11	9 Females, 2 Males	36	ChAdOx1 nCoV-19	CVST, splanchnic vein thrombosis, pulmonary embolism, aortoiliac thrombosis, concomitant thrombocytopenia	NR	5	A reduced dose of LMWH	6/11 (54.5%)
Abu Esba et al., 2021[14]	Saudi Arabia	Cohort	14	8 Females, 6 Males	30	AstraZeneca, Pfizer-BioNTech	Complete thrombosis of the left transverse sinus extending to the left sigmoid sinus and jugular vein	2=DM, 2=HTN, 1=HF, 1=COPD, 1=DLP, 1= high liver enzymes	7.8	Heparin followed by enoxaparin or apixaban	1/14 (7.1%)
Krzywicka et al., 2021[15]	Europe (various)	Cohort	213	158 Females, 55 Males	51	ChAdOx1 nCov-19, mRNA vaccine	Splanchnic vein thrombosis, pulmonary embolism, deep vein thrombosis, pelvic/renal vein thrombosis, vena cava thrombosis, retinal thrombosis	24=Any CVST risk factor reported, 17=OCP	8	NR	46/213 (21.6%)
Kammen et al., 2021[16]	Europe and various others	Cohort	116	93 Females, 23 Males	50	ChAdOx1 nCov-19, BNT162b2 (Pfizer/BioNTech), CoronaVac (Sinovac), Ad26.COV2.S, mRNA-1273 (Moderna)'	Concomitant thromboembolism	35=Conventional CVST risk factors*	8	Heparin, non-heparin anticoagulants, immunomodulation therapy (IV), endovascular treatment, decompressive hemicraniectomy	38/116 (32.8%)
Kerr et al., 2022[17]	England, Scotland, and Wales	Self-Controlled Case Series	8,130,614	4,396,967 Females, 3,733,647 Males	54.8	ChAdOx1, BNT162b2	NR	291,905=Stroke/TIA, 152,881=Thrombosis or pulmonary embolus, 97,257=Peripheral vascular disease	NR	NR	46,696/8,130,614 (0.6%)
Bikdeli et al., 2022[18]	Spain, Austria, Czech Republic, France, Israel, Italy, USA	Cohort	102	61 Females, 41 Males	66	Adenovirus-Based Vaccines (AstraZeneca, Johnson, and Johnsson), mRNA-Based Vaccines (Pfizer and Moderna)	Pulmonary embolism with or without DVT. Isolated DVT, Cerebral venous sinus thrombosis, Splanchnic vein thrombosis, Venous thrombosis in >1 territory	12= Coronary or peripheral arterial disease or ischemic stroke, 18=VTE	4-30*	Low-molecular-weight heparin, Argatroban/bivalirudin/danaparoid/fondaparinux, Fibrinolytic therapy	5/102 (4.9%)
Munckhof et al., 2022[19]	Europe (various)	Cohort	270	191 Females, 79 Males	46	Adenoviral vector-based vaccine (ChAdOx1 nCov- 19, Ad26.COV2)	NR	NR	<28*	NR	83/270 (30.7%)

Pregnancy and the first few weeks after delivery; Problems with blood clotting; for example, antiphospholipid syndrome, protein C and S deficiency, antithrombin III deficiency, lupus anticoagulant, or factor V Leiden mutation; Cancer; Collagen vascular diseases like lupus, Wegener's granulomatosis, and Behcet syndrome; Obesity; Low blood pressure in the brain (intracranial hypotension); Inflammatory bowel diseases like Crohn's disease or ulcerative colitis.

In total, 9 studies were included. They were conducted across USA, UK, Germany, Austria, and other European countries, Saudi Arabia, and Israel. Two of the included studies were case series, one was a self-controlled case series, and six were cohorts. In total, 8,131,391 were included in this synthesis. The total number of female participants was 4,397,516, meaning that 54.1% of the population was female. The overall mean age of all participants was 47.4 years with a standard deviation of 10.4. The site of thrombosis/concomitant conditions and risk factors are enlisted further in Table 1. The overall mean days after vaccination upon which the patients presented with CVST was 8 days with a standard deviation of 2.4. The participants were managed with various treatment modalities: Apixaban, Argatroban/bivalirudin/danaparoid/fondaparinux, Craniectomy, Cyclosporine, Decompressive hemicraniectomy, Dexamethasone, Eltrombopag, endovascular treatment, Enoxaparin, Fibrinolytic therapy, Heparin, IVIG, LMWH, Non-heparin anticoagulant agent, Platelets, Prednisone, RBC transfusion, Rituximab, Splenectomy (Table 1). The overall mortality rate among CVST patients was 25.4% (197/777).

DISCUSSION

The first batch of COVID-19 vaccines received emergency use authorization in September 2021, and more than 1.5 years have lapsed ever since. Although CVST may have grave outcomes among post-COVID-19 vaccinated individuals, this study finds that the incidence is a rare clinical event albeit with high mortality rates. In general, CVST is described as a vascular disease that occasionally affects the young women cohort with similar risk factors as with peripheral venous thrombosis.[20] At this juncture, it is difficult to entirely capsulate the true incidence and outcomes of CVST in the real-world vaccinated population because suspected or probable cases may have not been reported in current literature. A systematic review that collated evidence until the 4th of September 2021 identified 160 cases from 16 countries where the included patients were predominantly females; with a median age of 42.5 years.[21] The authors computed that symptoms of CVST presented on an average of 9 days post-vaccination.[21] The mortality rate was 36.2% and there were higher associations to death among patients that were not given non-heparin-anticoagulants, IVIG, or platelets.[21]

Since March 2021, cases of CVST have been reported in patients vaccinated with the Johnson and Johnson and Oxford-AstraZeneca ChAdOx1-S vaccines among others.[10] Evaluation by international bodies has concluded that there are plausible causalities between the adenovirus/mRNA vaccines and events. The association is computed based on temporal associations and increased incidence compared to the expected baseline rates.[10] It is imperative to note that thrombotic complications are at high frequency in patients with active or recent SARS-CoV-2 infection.[10] Thrombocytopenia, which is a condition with less than 150,000 platelets/uL, has been reported to occur in about 15% of COVID-19 patients with CVST. The relative risk of CVST among patients with SARS-CoV-2 compared to those without it is estimated to be at 14 times the general population's limit.[10] The mortality rate due to CVST in COVID-19 patients between 24 March 2020 and 1 March 2021 is computed to be 11.9% as per the World Health Organization (WHO). WHO also reports that the most frequent vaccine-related thrombotic syndrome is CVST which presents as a headache in 50% of cases, in addition to other signs and symptoms. Vaccine-related CVST also presents as intracranial hemorrhage in 40% of the patients.[10]

A population-based cohort study reports that most CVST occurs within 15 days after vaccination which is the highest at-risk period.[22] The postvaccination rate of CVST, as seen in other reports, is higher among females as compared to the pre-pandemic rate.[22] The highest risk is among women aged 30-49, but the absolute CVST risk is still low in this group (29.5/100,000 per year among women aged 40-49).[22] While the reason for the higher incidence of post-vaccination CVST is unclear, concomitant CVST risk factors or the production of autoantibodies may be the cause.[22] However, studies also find that coagulative disorders in pregnant and puerperal women were found to cause CVST, instead of manifesting as a DIC/HIT-like syndrome.[9,10] The hormonal alterations and amniotic fluid's thromboplastin-like material have also been suggested to trigger vascular thrombosis.[9,10,23] Oral contraceptives, cancer, chemotherapy, polycythemia, leukemia, and neurological disorders may instead emblematize hazardous conditions in the individual.[9,10,23]

Certain limitations ought to be addressed in this study. First, case reports were excluded hence certain information may be missing. Secondly, since case series were also included, the evidence may be considered mild-moderate. However, this systematic review collates evidence until March 10, 2022, and computes the most recent evidence of CVST incidence, clinical risk factors, prognosis, and outcomes. The findings of this study are intended to benefit both the healthcare and the general population as more vaccines are administered worldwide.

CONCLUSION

SARS-CoV-2 vaccine-induced CVST may occur at any age and gender, but the female population aged 30-49 is at high risk of suspicion if symptoms arise. While the WHO guidance states that CVST is more common with adenoviral vaccines, this study finds that mRNA vaccines also contribute to CVST. The disease is associated with a high mortality rate, and timely diagnosis, preferably within 15 days, may decrease adverse outcomes in patients. While healthcare providers ought to be cautious with symptoms' presentation, COVID-19 vaccinations are currently the first line in fighting against the pandemic. While mild concern may be required, excessive concern for post-vaccination headaches may be inappropriate. While this study establishes a correlation between COVID-19 vaccination and CVST, further exploration of causality is required as the pandemic progresses, and with newer waves of COVID-19 penetrating communities worldwide.

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