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Cerebral Venous Thrombosis (CVT) Following COVID-19 Vaccination: an Umbrella Review of Systematic Reviews

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ABSTRACT

Background and Aim: This umbrella review presents comprehensive data on the evidence of the association between cerebral venous thrombosis (CVT) and COVID-19 vaccinations.

Materials and Methods: We searched related databases to access issue-related systematic reviews both with meta-analyses and without it that studied the connotation between COVID-19 vaccination and CVT in any language on March 1, 2022. Two reviewers independently extracted the data using the JBI Form for Data Extraction in Systematic Reviews and Research Syntheses.

Results: The primary search resulted in 886 titles, and finally, 48 full texts were selected, and of these, 12 qualitative systematic reviews or quantitative meta-analyses were eligible for the umbrella review. No study was excluded based on using the JBI checklist for critical appraisal. The results revealed that cerebral venous sinus thrombosis (CVST) from the COVID-19 vaccine could occur in any age group, in both sexes, and with all types of vaccine. However, young females were the predominantly affected cases. Although more common in adenovirus vaccine types, vaccines consisting of mRNA are not free from side effects. Headache was the most typical clinical symptom. Thrombocytopenia, PF4 IgG Assay, and d-Dimer evaluation were positive in many reported studies.

Conclusion: The results showed that CVST from the COVID-19 vaccine can happen without age limitation for both sexes and all vaccine types. Although CVST is a life-threatening condition, early diagnosis and, most importantly, its management can be life-saving for patients. The overall balance of risk and benefit in favor of vaccination is positive in all of the included studies in the current umbrella review.

Keywords: COVID-19; COVID-19 Vaccines; Venous Thrombosis; Systematic Review

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1. Introduction

COVID-19 is a complicated disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), which rapidly spread and was announced as a severe pandemic in the world on March 11, 2020 **(1)**. The main transmitted way of this disease is the respiratory tract, commonly by respiratory droplets and aerosols **(2)**. A spectrum of mild to severe symptoms has been identified **(3-5)**, while most of the patients are asymptomatic.

Commonly reported disease symptoms are as follows: fever (83%), cough (82%), and dyspnea (31%); nevertheless, respiratory manifestations are not the only medical concern in this disease. According to the previous literature, COVID-19 is a multi-organ disorder with extrapulmonary manifestations including cardiovascular, renal, gastrointestinal **(6)**, hematologic **(7)**, and neurologic disorders (from simple headaches to more severe symptoms like acute cerebrovascular disease including cerebral vein thrombosis, disorders of consciousness, stroke, and seizure) **(1, 8)**.

Advances in vaccine development are crucial to prevent the rapid and vast spread of this viral infection and consequently decrease its mortality **(9, 10)**; therefore, many countries prioritize developing an effective vaccine against COVID-19 disease. There are several effective COVID-19 vaccines authorized and validated for global use by the world health organization (WHO). Besides Pfizer/BioNTech Comirnaty and Moderna COVID-19 (mRNA 1273) vaccines that are most evaluated in terms of effectiveness and safety, the SII/COVISHIELD and AstraZeneca/AZD1222 vaccines, Janssen/Ad26.COV 2.S vaccine developed by Johnson & Johnson, Sinopharm COVID-19 vaccine, Sinovac-CoronaVac vaccine, Bharat Biotech BBV152 COVAXIN vaccine, Covovax (NVX-CoV2373) vaccine, and Nuvaxovid (NVX-CoV2373) vaccine, have obtained WHO Emergency Use Listing Procedure till January 12, 2022.

COVID-19 vaccines had side effects, but most were mild to moderate and usually had short-term duration. These side effects are fever, fatigue, headache, myalgia pain at the vaccination site, shivering, and diarrhea. The probability of occurring any of the different side effects post-vaccination strongly depends on the type of vaccine **(11)**.

Another reported side effect after vaccination is Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) which is usually accompanied by cerebral venous thrombosis (CVT) **(12)**. CVT considers a type of stroke in which thrombosis in blood circulation results in occlusion of one or multiple cerebral veins and dura sinus. The incidence of CVT in Western Europe is 1.32/100000 persons in one year **(13)**. The incidence of CVT in developing countries and women is much more. CVT has variable clinical features; in mild cases, it could induce headaches, headaches with Papilledema or other elevated intracranial pressure symptoms, and focal symptoms like aphasia or paresthesia usually associated with the seizure. In severe cases, symptoms might involve encephalopathy, coma, or status epilepticus. The definitive test for diagnosing CVT is magnetic resonance imaging (MRI) of the head **(14)**.

Different risk factors for CVT can be categorized as follows:

1- Temporary risk factors: such as oral contraceptive drugs (OCPs) and other drugs with prothrombotic effects, pregnancy and the postpartum period, infections, and most importantly, those which affect the central nervous system, ears, paranasal sinuses, and mastoid bones.

2- Permanent risk factors: thrombophilic genetic disease, antiphospholipid disease, malignancies, and myeloproliferative disorders.

However, about 13% of adults with CVT have no known risk factors. According to statistics, the CVT mortality rate in the Western world is below 5%, and around 80% of these patients recover entirely **(15, 16)**. With the widespread global vaccination against Covid-19 disease, further comprehensive studies in this field are required to prevent and manage its different complications **(17, 18)**.

Given that some studies have demonstrated a significant association between the incidence of CVT and COVID-19 vaccination and also, several cases of CVT have been reported following receiving various types of COVID-19 vaccines and the importance of vaccination to combat this pandemic and considering the other published systematic review and meta-analysis, this umbrella review of systematic reviews present a comprehensive view of the evidence concerning the relation of CVT and COVID-19 vaccinations.

2. Materials and Methods

An umbrella review comprehensively focuses on existing evidence that systematically searches, evaluates, and organizes from numerous systematic reviews (with/without meta-analysis) on consequences detected correlated with intended exposure **(19)**. For this purpose, Joanna Briggs Institute (JBI) instructions were followed to carry out this umbrella review. Because of the lack of meta-analysis studies in this field and presenting the data

in the qualitative reports, only systematic reviews that didn't have meta-analysis are included in the current study.

Literature Search

We systematically searched PubMed, Medline (via Ovid), Embase (www.embase.com), CINAHL (via EBSCO), Epistemonikos, the JBI Database used for searching Systematic Reviews and Implementation Reports, the Cochrane-related Database for searching Systematic Reviews, the Database searching Abstracts of Reviews, Scopus, the PROSPERO register, and Web of Science to identify related systematic reviews both with/without statistical meta-analyses with focusing on any correlation between COVID 19 vaccination and CVT in Different types of languages from beginning to March 1, 2022. Also, we searched Google Scholar to find any potentially related records. The Medline search strategy is attached as Appendix 1. Finally, we used a hand search process in the reference list of included studies. Screening of the titles and abstracts was done by two authors independently and then chose the related full texts. In the case of the author's disagreement, a third independent author arbitrated.

Eligibility Criteria and Data Extraction

This review only includes systematic reviews with/without systematic meta-analysis. We just included systematic qualitative reviews. No limitations were applied regarding the population sample size, ethnicity, study setting, type of race, or origin country. The studies compared the risk of rising CVST, or CVT, in individuals receiving COVID-19 vaccination.

Two independent reviewers have done the related data extraction from the included articles. Reviewers have done data extraction based on the JBI Specific Data Extraction Form used in the Systematic Review studies and Research Syntheses **(19)**. The extraction list includes the author's name, the publication year of study, the objective, the total characteristics of the contributors, the total number of included studies or contributors, sources or range searched, study type, critical appraisal scoring, and instrument. Any possible differences between the two independent reviewers were debated and resolved by consensus between all of the co-authors.

Evaluation of Methodological Quality and Quality of Evidence in Included Studies

We evaluated the methodological quality of all included systematic reviews using the JBI-established critical appraisal tools for systematic reviews to address and reduce bias **(20)**. If any study achieved less than five 'yes' responses, authors were excluded from the study.

3. Results

Figure 1 comprehensively shows eligible studies' systematic search and process of selection for the current umbrella review. In the early search, we identified 886 titles, and after eliminating the duplicated articles, reviewing the 640 titles and abstracts was started. Finally, we selected 48 full texts, and of these, 12 systematic qualitative reviews of quantitative meta-analyses were considered eligible for doing this umbrella review (Figure 1).

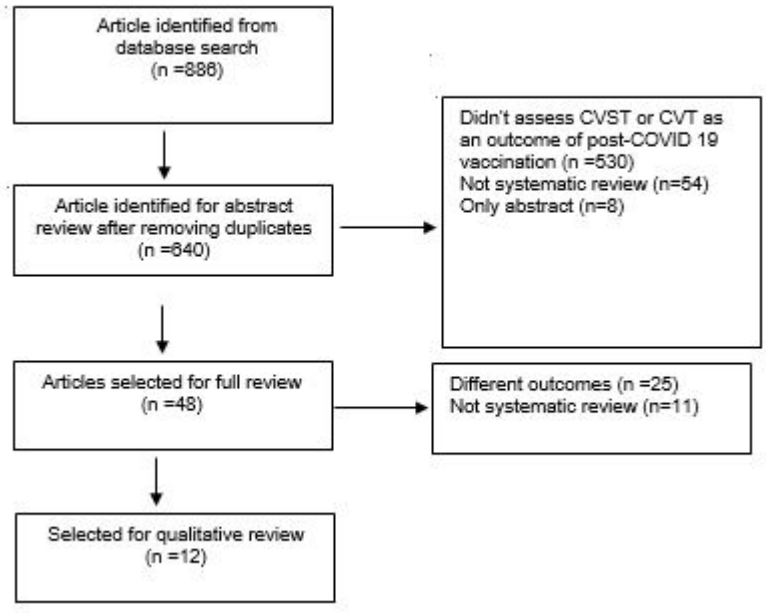

Figure 1. Flowchart of selection of studies for inclusion in the umbrella review

We evaluated the quality of the studies using the JBI questionnaire to perform the critical appraisal of included systematic reviews. All of the included studies received more than five 'yes' answers, so none of the studies were excluded. An overview of the 12 eligible studies' risk assessments is shown in Table 1.

Table 1. Joanna Briggs Institute questionnaire for critical appraisal of systematic reviews

Question	Study											
	Sharifian-Dorche M (2021)	Dotan A (2021)	Chen J (2021)	Bignucolo A (2021)	Palaiodimou L (2021)	Wu Q (2021)	Jaiswal V (2022)	Aghabaklou S (2021)	Elberry M (2022)	Hafeez M (2021)	Matar R (2022)	Waqar U (2021)
1. Is the review question clearly and explicitly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were the inclusion criteria appropriate for the review question?	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the search strategy appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were the sources and resources used for the study adequate?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
5. Were the criteria for appraising studies appropriate?	No	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Unclear
6. Was critical appraisal conducted by two or more reviewers independently?	No	No	Yes	Yes	Yes	Unclear	No	No	Yes	No	Yes	Unclear
7. Were there methods to minimize errors in data extraction?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were the methods used to combine studies appropriate?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the likelihood of publication bias assessed?	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No

Question	Study											
10. Were recommendations for policy and/or practice supported by the reported data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the specific directives for new research appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall appraisal	include	include	include	include	include	include	include	include	include	include	include	include

The quantitative results of the studies are presented in Table 2, which is demonstrated the data summary of the included systematic review and meta-analysis.

Table 2. Tabular presentation of qualitative findings for an umbrella review.

Author/ year	Number of studies/participants	Vaccine	Outcome	Time from vaccination (days)	Clinical presentation	Total no./sex/age	Imaging findings	Lab findings
Sharifian-Dorche M (2021)(21)	14/54	AstraZeneca COVID-19 vaccine (ChAdOx1)	12 articles, which present the clinical features of 41(36 CVST, 4 infarctions, 1 ICH) patients. Among 36 patients with CVST, 16 patients had an ICH and/or Subarachnoid Hemorrhage (SAH) (44%). Of all reported cases (41 patients), 18 (44%) died.	7 days, range (4–19)	Headaches most frequent	41 In 32 patients, sex was reported (23 F, 9 M)	CVST:36 MCA infarct: 4 ICH:1 (CVST+ICH /SAH: 16)	Platelet count: 39 cells×109 /l (5–113) PF4 IgG Assay: Positive: 27 Negative: 2 Unknown:11 d-Dimer: Positive: 35 Unknown:5
		Johnson & Johnson COVID-19 vaccine (Ad26.COV2)	Two articles present 13 patients. All of these patients were females. Among 13 reported patients with CVST, eight patients had ICH/SAH (61%).	9.2 days, Range (6–14)	Headache most frequent	13 F	CVST:36 MCA infarct: 4 ICH:1 (CVST+ICH /SAH: 16)	Platelet count: 39 cells×109 /l (5–113) PF4 IgG Assay: Positive: 27 Negative: 2 Unknown:11 d-Dimer: Positive: 35 Unknown:5
		Alive:21 Died:18(16 CVST, 1 ICH, 1 Infarct) Unknown:2						
Dotan A (2021)(22)	4/41	ChAdOx1	17 out of the 41 patients (41.4%) had died, mostly as a result of hemorrhagic or ischemic brain injury.	5–24 days after the first dose of vaccination	Headache most frequent	27 F (21–77 years old)		PF4 IgG Assay: Positive: 36 of the 38 (94.7%) Platelet count: 30,000–40,000/m3, with a range of approximately 10,000 to 110,000. Very high levels of d-dimers and

Author/ year	Number of studies/participants	Vaccine	Outcome		Time from vaccination (days)	Clinical presentation	Total no./sex/age	Imaging findings	Lab findings
									low levels of fibrinogen
Chen J *(23)	23 studies	Inactivated vaccine	*Although 17 cases of cerebrovascular events were recorded, no definite CVT was reported.	Vaccine: 2 out of 12021 Control: 4 out of 11724	7 days Range (14 or 28 days)	Headache most frequent (98.2%)	NM	NM	NM
		Replicant incompetent vectors vaccine		Vaccine One dose: 3 out of 16427 Two doses: NA Control One dose: 2 out of 5435 Two doses: NA					
		mRNA		Vaccine: 5 out of 15185 Control: 1 out of 15166					
Bignucolo A (2021)(25)	6/6736 healthy subjects were included in the safety analysis of (3252 F 3484 M)	Ad26.COV2.S-Johnson & Johnson/Janssen vaccine	Thrombotic events included deep vein thrombosis, pulmonary embolism, and transverse sinus thrombosis/cerebral hemorrhage. Specifically	10/11 (90.9%) cases of such adverse reactions were reported in the vaccine group for males and 1/11 (9.1%) for females, while 3/3 (100%) cases in the placebo arm all occurred in males		NM			
Palaiodimou L (2021)(26)	69/4182	SARS-CoV-2 vector-based vaccine	370 cases of CVST: Among TTS cases, the pooled proportion of CVST was 51% (95% confidence interval [CI] 36%–66%; I^2= 61%). TTS was independently associated with a higher likelihood of CVST when compared to patients without TTS with thrombotic events after vaccination (odds ratio 13.8; 95% CI 2.0–97.3; I^2 = 78%). CVST: in 29% of the patients presenting with any thrombotic event after administration (95% CI		2 weeks with mean 10 days, range (8–12)	NM	The mean age of patients with postvaccination CVST and TTS–CVST was ≤45 years; (2) there was a striking (≥75%) female prependerance among CVST cases irrespective	NM	The pooled proportion of thrombocytopenia among CVST cases was 70% (95% CI 59%–80%; 7 studies; I^2 = 37%; p for Cochran Q = 0.145); The proportion of thrombocytopenia among patients with any

Author/ year	Number of studies/participants	Vaccine	Outcome		Time from vaccination (days)	Clinical presentation	Total no./sex/age	Imaging findings	Lab findings
			18%–41%; 15 studies; I^2=95%; p for Cochran Q< 0.001). When only TTS-associated cases were considered, the pooled proportion of CVST cases among all thrombotic events was (51%; 95% CI 36%–66%;1^2 studies; I2=61%; for Cochran Q= 0.003				of the presence of concomitant thrombocytopenia;		thrombotic event was 46% (95% CI 17%–77%; 9 studies; I^2 = 98%; p for Cochran Q<0.001); PF4 IgG Assay: Positive: 91% (95% CI 83%–97%;11 studies; I^2=18%; p for Cochran Q=0.274) of TTS-associated CVST cases; 87% (95% CI 76%–95%; 13 studies; I^2=53%; p for Cochran Q=0.013) of the patients with TTS-associated thrombotic event
Wu Q (2021) (24)	87 studies	TTS (Thrombosis with thrombocytopenia syndrome)			NM	NM	NM	NM	NM
		COVISHIELD/AstraZeneca	46 out of 50 cases	6 people died.					
		Pfizer	3 out of 50 cases						
		Moderna vaccine	1 out of 50 cases						
		Oxford/AstraZeneca	1 death out of 208 SAEs due to thrombosis of the cerebral venous sinus						
Jaiswal V (2022)(27)	25/80 CVST cases	AstraZeneca (ChAdOx1 nCoV-19	54 (66.3)	Mortality outcome: 31 (38.8)	11.10 (5.34)		59F 21M	NM	Mean (SD) Platelet count: 46113 (57670) PF4 IgG Assay: Positive: 45 (56.3%)
		Johnson & Johnson/Janssen (Ad26.COV2.)	16 (20.0)						
		Pfizer BioNTech (BNT162b2 mRNA)	7 (8.0)						
		Moderna (mRNA-1273)	4 (5.0)						
Aghabaklou (2021)(28)	23/66 CVST cases	AstraZeneca (ChAdOx1 nCoV-19)	Alive:24 Fatal:25 Unknown:2 2 Patients on OCP		9.1 days Range: (4-19)	Headaches (most frequent complaint)	51 In 42 patients, sex was reported (28 F, 14M)	CVST:45 MCA infarct: 4 ICH:4 (CVST+ICH /SAH: 19)	Platelet count: 50 cells×10^9/lit (5-113) PF4 IgG Assay: Positive: 35 Negative: 3 Unknown:11 d-Dimer: Positive: 43 Unknown:5
		Ad26.COV2.S (Johnson &	Discharged: 5 Fatal: 4		10.4(Range: 6-	Headache most	15 F	15 CVST CVST+ICH/	Platelet count: Mean:

Author/ year	Number of studies/participants	Vaccine	Outcome	Time from vaccination (days)	Clinical presentation	Total no./sex/age	Imaging findings	Lab findings
		Johnson/ Jansen)	Critically ill:4 6 Patients with Obesity One on OCP Non-ICU hospitalization:2	14)	frequently presenting complain		SAH: 10)	43 cells×10^9/lit (Range:9-127) PF4 IgG Assay: Positive in 12 cases Unknown in 2 cases d-Dimer: 15 Positive in all cases
Elberry M (2022)(29)	26/173	ChAdOx1 nCoV-19 (n=157)	18 (11.5%) CVST; 15 (9.6%) CVT	10.5	Headache most frequently presenting complain	72% F	NM	Platelet count: 33,500 cells/mm3 (7000–334,000) in 62 pts; D-dimer elevated in 52(33.1%) pts; PF4 Ab: positive in 39(24.8%) pts; The median fibrinogen: 1.2 g/liter (0.4–5.7) in 62pts
		Ad26.COV2. S (n=16)	14 (87.5%) CVST; 1 (6.3%) CVT	15.9		100% F	NM	20,000 cells/mm3 (9000–127,000) in 16 pts; D-dimer elevated in 15(93.7%) pts; PF4 Ab: positive in 13 (81.2%) pts; The median fibrinogen: 141 (59–332) in 16 pts.
Hafeez M (2021)(30)	25/69	Single dose of AstraZeneca (ChAdOx1 nCoV-19): (N=51, 73.9%) was administered to 20 (83.3%) individuals who died (P=.136).	Total sample (N=69): CVST=47 (68.1%); Alive (N=45): CVST =27 (60%); Dead (N=24): CVST =20 (83.3%). Platelet nadir (P<0.001), arterial or venous thrombi ($\chi2$=41.911, P=0.05), and chronic medical conditions ($\chi2$=25.507, P=0.041) were statistically associated with death. The ROC curve analysis yielded D-dimer (AUC =0.646) and platelet nadir (AUC=0.604) as excellent models for death prediction. There were 51 females (73.9%) in the total sample, with 80% who remained	10.4±8.14 in the alive group and 7.67 ±5.95 in the dead group (P=0.109).		51 (73.9%) F		Anti-PF4/heparin antibodies were present in 53 (76.8%) patients, and they were more prevalent (87.5%) in the individuals who died (P=0.416). The median value of platelet nadir (109/L) among the entire

Author/ year	Number of studies/participants	Vaccine	Outcome		Time from vaccination (days)	Clinical presentation	Total no./sex/age	Imaging findings	Lab findings
			alive and 62.5% who died (*P*=0.059).						sample was 326, ranging from 8 to 334 (*P*< 0.001). The median D-dimer peak (mg/L) value among the population was 140.9, ranging from 1.1 to 142 (*P*=0.419).
Matar R (2022)(31)	45/144	AstraZeneca	CVST in 38.5%	A total of 78 patients recovered, while 39 patients died.	8.468 days (95% CI 7.486–9.451; I^2=79.42%) ranging from 0 to 20 days	Headache (12.1%; 95% CI 0.095–0.154, I2¼0%), intracerebral hemorrhage, hemiplegia, fever, congestive edema, visual impairment, and ocular manifestations	64.6% F	The most common radiologic findings were ICH and CVT.	Thrombocytopenia (75%) and hypofibrinogenemia (41%). On admission, 64 patients tested positive for PF4-Heparin ELISA assay (80%).
Waqar U (2021)(32)	62/160	AZD1222 was administered to 140 patients (87·5%). Ad26.COV2.S in 20 pts.	CVST; 66.3%. TTS predominantly occurred after the first dose (76/77, 98.7%), while dosages were unknown for the remaining 63 patients.	CVST was significantly more common in female vs. male patients (*P*=0·001) and in patients aged <45 years vs.≥45 years (*P*=0·004). mortality rate was 36.2%,	median of 9 (4; N=131) and 11 (5; N=113)	Visual defects, severe headaches, leg and back pains, easy bruising, or petechiae.	The majority of TTS patients were females, those aged 30–49 years, and those without any known comorbidities.	NM	PF4 IgG Assay: Positive: 120 pts (100%); thrombocytopenia in all tested pts; Many patients had elevated levels of D-dimers, PT, TT, and INR with low fibrinogen levels. Antiphospholipid antibodies were assessed in 71 (44·4% [71 of 160]) and were positive in 4 patients (5·6% [4 of 71]).

Sharifian-Dorche **(21)**, in a systematic review, reported 36 CVST, 16 ICH or Subarachnoid Hemorrhage (SAH) cases, and 18 (44%) death in these patients. Most of the study population was women, and symptoms were

stated to happen within one week after receiving the first vaccine dose with a range of 4–19 days. Headache was the most common symptom, which was present in the patients. Most patients present positive Thrombocytopenia, PF4 IgG Assay, and d-Dimer.

Dotan **(22)** reported the thrombosis outcomes of 4 studies on 41 thrombotic thrombocytopenia cases induced by ChAdOx1 nCov-19 vaccines. During 5–24 days following receiving the vaccine (the first dose), a development in the production of thrombosis accompanied by thrombocytopenia was reported.

Chen **(23)**, evaluated the overall incidences of nervous and muscular adverse events (NMAEs) following receiving the COVID-19 vaccine. In 15 phase 1/2 trials, NMAEs happened in 29.2% of vaccinated participants and 21.6% of controls (P<0.001). Headache (98.2%) was present with an incidence of 16.4% vs. 13.9% in the vaccine and control groups, respectively, with more commonly in the vaccines that newly licensed and younger adults. However, they concluded that although 17 cases of cerebrovascular events were recorded, no definite CVT was observed.

Wu **(24)** performed a rapid review of 87 publications and reported the pooled rates of local and systemic reactions in different platforms. According to their findings, these side effects were meaningfully lesser between all inactivated types of vaccines (23.7%, 21.0%) and higher in virus-like particle types (100.0%, 78.9%).

Bignucolo **(25)** reported the non-fatal and most serious adverse event of mRNA-1273-Moderna and venous thromboembolic events Ad26.COV2.S-Johnson & Johnson/Janssen in their systematic review, including six studies. In terms of venous thromboembolic events, the results showed that various thrombotic events such as deep vein thrombosis, embolism in the pulmonary system, transverse sinus thrombosis, or other cerebral hemorrhage have occurred in 10/11 (90.9%) studied cases in the group that received the vaccine for males and 1/11 (9.1%) for a vaccinated group of females. In contrast, in 3/3 (100%) cases in the placebo group, all of these events happened among males, and only one male suggested that deep venous thrombosis occurred because of vaccine administration.

Palaiodimou **(26)**, in a systematic review including 69 studies on 4182 cases, comprising 370 patients with CVST with any thrombotic symptom related to the administration of SARS-CoV-2 vector-based vaccine, showed that between TTS cases, the CVST pooled proportion reported 51%. They concluded that TTS was independently accompanied by a higher possibility of CVST than patients without TTS. The pooled mortality rate of TTS was 28%, and TTS-associated CVST was 38.

Jaiswal **(27)**, in a systematic review of 25 studies consisting of 80 CVST patients after COVID-19 vaccination, showed that 31 patients died, without any association with age or sex, vaccine type, platelet count, underlying diseases including hypertension and diabetes mellitus (P>0.05). However, the beginning of CVST symptoms after vaccination was associated with mortality, and treatment with anticoagulants in these cases decreased the mortality rate. In these cases, the other mortality risk factors were intracranial hemorrhage or thrombosis in the location of the cortical vein.

Aghabaklou *et al.* **(28)**, in their systematic review, reported 66 patients who presented CVST and VITT after two adenoviral vector vaccination. Among the cases, 86% of the patients showed the above-normal D-dimer. Furthermore, 68% of the evaluated patients showed a positive platelet factor 4 IgG assay since they didn't have exposure to heparin priorly. The authors concluded that early diagnosis of these cases and rapid treatment of CVST played a fundamental role in declining the rate of morbidity and mortality.

Elberry *et al.* **(29)**, showed thrombotic events following receiving the ChAdOx1 nCoV-19 vaccine, and 16 patients showed thrombotic events post-vaccination with Ad26.COV2. S. Most ordinary presentations in the ChAdOx1 nCoV-19 subgroup were thrombosis in the deep vein and thrombosis in the cerebral venous sinus, while Ad26.COV2. S subgroup presents the most common complications via thrombosis in the cerebral venous sinus; the other was a pulmonary embolism.

Hafeez *et al.* **(30)** included 25 studies (overall patient= 69) in their systematic review and performed a post hoc analysis. Various complications, including; chronic medical conditions, platelet nadir, and predominantly arterial or venous thrombi, were statistically associated with death.

In Matar's **(31)** study, the included studies were 45 of 144 patients, including 64.6% women; the most commonly observed adverse events were headache (12.1%), hemiparesis, and intracerebral hemorrhage. The most common thromboembolic adverse events were CVST (38.5%) and thrombosis in a deep vein or pulmonary embolism (21.1%). Intracerebral hemorrhage and CVT were the most common radiologic finding. Similar to the previous systematic reviews, thrombocytopenia, and hypofibrinogenemia were among the common laboratory findings, besides positive PF4-Heparin ELISA assay.

Waqar U **(32)** concluded that CVST was more common in females below 45. The mortality rate was 36.2%, and the likelihood of expiring than recovery was more in the patients with suspected TTS, severe venous thrombosis, CVST, pulmonary embolism, or intraneural dysfunctions, patients who were not managed with non-heparin anticoagulants or IVIG, patients who received platelet transfusions, and most importantly patients who

require to admission in the intensive care unit, need mechanical ventilation, and inpatient receiving neurosurgery.

4. Discussion

Our findings showed that although all vaccines in the systematic reviews included in the current umbrella review have resulted in cases of CVST, most cases of CVST were observed after COVID-19 vaccination in patients receiving AstraZeneca and Johnson & Johnson/Janssen, which was in accordance with reports that previously announced the Centers for Disease Control and Prevention (CDC). There are also findings of an increased incidence of CVST following AstraZeneca and Johnson & Johnson vaccination after COVID-19 compared to pre-epidemic incidence.

Thrombocytopenic thrombocytopenia post-vaccination is not considered a new phenomenon in vaccine side effects **(33)**. One of the first reports in 1973 was about thrombotic thrombocytopenia after receiving the influenza vaccine **(34)**. Similar events have been shown after H1N1, pneumococcal, and rabies vaccination **(35-37)**. These reports suggested that corticosteroids, rituximab, and plasmapheresis could be an effective treatment strategy. Nevertheless, in none of these patients, CVST was observed **(37)**.

The increase in incidence can be clarified by the pathophysiological alterations supposed to happen in VITT. Definitive VITT is well-defined by the American Hematological Association as a clinical syndrome with criteria for the beginning of symptoms 4-42 days following COVID-19 vaccination; including thrombosis preparation in Venous or artery in all areas, exclusively in unusual locations such as CVST; reduction (Mild to moderate) in platelet count (fewer than 150,000 mm3); PF4-positive antibody evaluated by ELISA; an increase in D-dimer equal to or greater than 4000 FEU causes CVST after COVID-19 vaccination and is confirmed with the presence of anti-PF4 antibodies and also with low-level platelet count, which was reported in all studies that defined laboratory criteria for the CVST cases **(38)**.

VITT has similar clinical features to heparin-induced autoimmune thrombocytopenia (HIT). Furthermore, HIT is produced by platelet-activating immunoglobulin G (IgG) antibodies against heparin-complexed platelet factor 4 (PF4). Free DNA is thought to bind to PF4 in adenovirus-based vaccines, including AstraZeneca and Johnson & Johnson/ Janssen, producing reactive PF4 antibodies **(38, 39)**.

This unique complex finally binds to platelet FcRγIIA receptors, activating platelets and forming platelet microparticles **(40)**. These microparticles begin to form blood clots, then trigger a prothrombotic cascade, which leads to a reduction in the number of platelets and induces thrombocytopenia. In addition, the reticuloendothelial system, mainly the spleen, affects removing the antibody-coated platelets, finally exacerbating thrombocytopenia **(40, 41)**. Furthermore, it has been shown that some cases with approved clinical signs and laboratory characteristics of HIT are referred to as autoimmune HIT even though they have not previously received heparin. The sera of these patients mostly contain antibodies that lead to activation of platelets even in the situation of lack of heparin. Most of the patients with spontaneous HIT have been reported before orthopedic surgery (release of glycosaminoglycan or cartilage RNA of the knee because of the cell damage related to tourniquet) or infection (exposure to microorganisms) **(42)**. Vaccine-platelet interactions or PF4 may be involved in the VITT pathogenesis. A probable description for this event is the binding of the free DNA in vaccines to PF4, which progressively stimulates PF4-reactive autoantibodies in VITT settings. The predominance of thrombosis in the brain's venous sinuses was observed, which was one of the critical observations in VITT vaccination after Covid-19. Although, HIT is a prothrombotic condition; however, there is no evidence to show that it could be preferentially associated with CVST. In addition, using brain imaging in the patients that received the COVID-19 vaccine associated with VITT and CVST revealed high levels of ICH and SAH **(43)**.

Recognizable risk factors for thrombosis were observed in patients, like female gender, pregnancy period, autoimmune disorders, puerperium, oral contraceptives, and hormone replacement therapy in women **(21, 44-46)**. In addition, one of the probable factors that lead to increment risk of CVST among females may be due to the higher rate of vaccination in women than men, but these observations are consistent with experience with risk factors for CVST **(47)**.

Our results showed that most cases have occurred in people under 60 years of age within two weeks of receiving the vaccine for the first dose.

The diagnosis process can sometimes be challenging. Symptoms of CVST may be similar to other types of neurological dysfunctions and may reflect the location of the vein or sinus involved **(21)**. Nevertheless, headache is a common symptom and was observed in most patients **(44)**. Progress in focal neurological defects was observed following the disease progress, which is due to venous infarction and seizures, the phenomenon that is more commonly seen in CVST than in other types of stroke.

Complete recovery may occur with timely diagnosis and treatment **(48)**. Interestingly, COVID-19 infection is a critical risk factor for occurring CVST and, compared to COVID-19 mRNA vaccines (Pfizer and Moderna), is more likely to result in CVST **(49)**. The results of the current umbrella review presented all included systematic reviews with acceptable methodology quality. In addition, most of the included studies reported that CVT is a rare adverse event following any type of COVID-19 vaccination in any age or sex. However, a typical thrombosis, especially CVST called VITT, was more prevalent in young female subjects and diagnosed by low platelet count (<150 × 109/L), increase in plasma D-dimer levels (>0.5 mg/L), accompanied by a positive experimental test for anti-PF4 (platelet factor 4) antibodies. CVT was manifested at 4-28 days post-COVID-19 vaccination, and the common manifestation was a headache. Therefore, regarding mortality of this condition, approximately in half or situationally in more affected patients, timely identification for early diagnosis and, most prominently, accurate management of VITT is essential.

5. Conclusion

The overall balance of risk and benefit in favor of vaccination is positive. CVST from the COVID-19 vaccine can happen at various ages, in both sexes, and with multiple vaccines. As a result, our findings suggest that CVST is related to a high mortality rate. Early diagnosis and, most importantly, its management can be life-saving for patients.

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Ethics Approval

The current study is derived from the thesis of a medical student and approved by the regional ethic committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1400.712).

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' Contributions

K Sh, H SPM: project development, Manuscript revision, and supervision. H SPM, Gh F, H S, S A, N M, N A: Data Collection, Manuscript writing. All authors read and approved the final version of the manuscript.

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