Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

# COVID-19 vaccine-induced immune thrombotic thrombocytopenia: a review

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Rare but serious thrombotic incidents in relation to thrombocytopenia, termed vaccine-induced immune thrombotic thrombocytopenia (VITT), have been observed since the vaccine rollout, particularly among replication-defective adenoviral vector-based severe acute respiratory syndrome coronavirus 2 vaccine recipients. Herein, we comprehensively reviewed and summarized reported studies of VITT following the coronavirus disease 2019 (COVID-19) vaccination to determine its prevalence, clinical characteristics, as well as its management. A literature search up to October 1, 2021 using PubMed and SCOPUS identified a combined total of 720 articles. Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline, after screening the titles and abstracts based on the eligibility criteria, the remaining 47 full-text articles were assessed for eligibility and 29 studies were included. Findings revealed that VITT cases are strongly related to viral vector-based vaccines, which are the AstraZeneca COVID-19 vaccine (95%) and the Janssen COVID-19 vaccine (4%), with much rarer reports involving messenger RNA-based vaccines such as the Moderna COVID-19 vaccine (0.2%) and the Pfizer COVID-19 vaccine (0.2%). The most severe manifestation of VITT is cerebral venous sinus thrombosis with 317 cases (70.4%) and the earliest primary symptom in the majority of cases is headache. Intravenous immunoglobulin and non-heparin anticoagulant are the main therapeutic options for managing immune responses and thrombosis, respectively. As there is emerging knowledge on and refinement of the published guidelines regarding VITT, this review may assist the medical communities in early VITT recognition, understanding the clinical presentations, diagnostic criteria as well as its management, offering a window of opportunity to VITT patients. Further larger sample size trials could further elucidate the link and safety profile.

**Keywords:** COVID-19 vaccine, Viral vaccines, Thrombocytopenia, Thrombosis, Prevalence

## Introduction

In the past years, the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed many lives throughout the world. This necessitated the development of COVID-19 vaccines as one of the ways to curb and reduce the disease burden. Owing to the advancement in technologies and knowledge, COVID-19 vaccines were produced and manufactured in a short amount of time. Reactions at the site of injection, headache, fatigue, myalgia, and fever are the most commonly reported adverse events following COVID-19 immunization [1].

However, several rare but serious and potentially lethal thrombotic incidents in relation to thrombocytopenia, termed vaccine-induced immune thrombotic thrombocytopenia (VITT), have been observed since the vaccine rollout, particularly among replication-defective adenoviral vector-based SARS-CoV-2 vaccine recipients [2], with 15.8 cases and 2.1 cases detected per million persons receiving the first and second doses of AstraZeneca ChAdOx1 nCoV-19 vaccine, respectively [3], and 3.2 cases per million found among Janssen Ad26.COV2.S vaccinees [4]. Cases of VITT can also be seen in the messenger RNA (mRNA) vaccine, albeit to a much lesser extent than with the viral vector-based vaccines. To date, only seven cases have been discovered from the Moderna mRNA-1273 vaccine and 32 reports involved the Pfizer BNT162b2 mRNA vaccine [3]. Even when treated promptly, the blood clots emerging from VITT are aggressive and have a high possibility of causing death or severe impairments [5].

A notable feature of this syndrome is that the thrombosis commonly arises in atypical locations such as the cerebral or splanchnic (splenic, portal, mesenteric, hepatic) veins [6-10]. In some patients, thrombosis develops at the more common sites including the deep veins of the lower limb and pulmonary arteries [6-10]. In addition, arterial thrombosis, which can result in ischemic stroke and peripheral arterial occlusion, has been reported among VITT patients [11].

In diagnosing VITT, the presence of thrombosis, thrombocytopenia, and markedly high D-dimer values in the timeframe of 4 to 42 days following the COVID-19 vaccination, coupled with a positive anti-PF4 enzyme-linked immunoassay (ELISA) test, strongly indicate VITT and confirm the diagnosis, particularly in the absence of functional testing [12-14]. Confirmatory functional testing such as a serotonin release assay (SRA) may be executed to supply additional data and is valuable in diagnosing complex cases of VITT [15].

Various radiological imaging tools were employed to confirm the thrombotic event in VITT patients. These include brain computed tomography angiography (CTA), magnetic resonance imaging (MRI), and magnetic resonance venography (MRV) to detect cerebral venous sinus thrombosis (CVST) [16]. In recognizing the presence of an ischemic stroke (IS), a brain magnetic resonance angiogram (MRA) or head computed tomography (CT) was used [16]. CT pulmonary angiography (CTPA) was commonly utilized in verifying pulmonary embolism (PE) [16]. Doppler ultrasonography was carried out to identify deep vein thrombosis (DVT) [16]. Splanchnic vein thrombosis (SVT), on the other hand, can be confirmed with Doppler ultrasonography, an abdominal CT, or pelvis CT [16]. In term of its management, intravenous immunoglobulin (IVIG) and non-heparin anticoagulant are usually employed in treating this syndrome [12,15,17-21].

The objectives of this study include critically reviewing the prevalence of COVID-19 VITT cases reported worldwide. Apart from that, the clinical characteristics and management of COVID-19 VITT were assessed.

As there is emerging knowledge on and refinement of the published guidelines regarding VITT, this review may assist the medical communities in early VITT recognition and optimal intervention, offering a window of opportunity to VITT patients.

## Materials and Methods

For the searching strategy, the author performed a literature search by using two online databases, SCOPUS and PubMed. The search comprised English-language articles or reports published between 2019 until 2021 by using Boolean operator, truncation, and a combination of keywords such as "COVID-19 Vaccine," "Thrombocytopenia," "Thrombus Thrombocytopenia," "Prevalence", and "Management." The abstracts and titles of the articles were evaluated for the purpose of screening and inclusion. During the preliminary title screening, the following English articles or reports related to the keywords were included: original articles, research articles, case reports, case series, brief reports, correspondence, and short communications. Meanwhile book chapters, review articles, commentaries, encyclopedias, letter to editors, and non-English articles were excluded. Then, the articles or reports were assessed for eligibility, with only studies that exclusively focused on VITT and studies that presented at least one case of VITT being chosen. The data from each selected article were stored and analyzed in Microsoft Excel software (Microsoft Corp., Redmond, WA, USA) for the purpose of data extraction.

## Calculation of Prevalence among the Included Studies

The prevalence of VITT cases following each COVID-19 vaccination was calculated by dividing the number of patients who developed VITT after each COVID-19 vaccination (AstraZeneca COVID-19 vaccine [n=429], Janssen COVID-19 vaccine [n=18], Moderna COVID-19 vaccine [n=1], and Pfizer COVID-19 vaccine [n=1]) by the total of VITT cases (n=450) and multiplying by 100. The prevalence of CVST cases among

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VITT patients was calculated by dividing the number of VITT patients who developed CVST following COVID-19 vaccination (n=317) by the total of VITT cases (n=450) and multiplying by 100. The percentage for mortality of the VITT patients was calculated by dividing the number of VITT patients for each outcome (alive [n=309], died [n=137]) by the total number of VITT patients (n=450) and multiplying by 100.

## Results

The literature search was conducted from 14th October 2019 until 9th October 2021, and identified a combined total of 720 articles. After screening the titles and abstracts based on the exclusion criteria, the remaining 47 full-text articles were assessed for eligibility and 29 studies were included (Fig. 1). The demographic, clinical characteristics, laboratory findings, and outcome of patients with VITT from the published studies are displayed in Tables 1–4. Pharmacological and non-pharmacological management used by the gathered studies are illustrated in Table 5.

From the 29 studies included, there are a total of 18 case reports, six case series, and five retrospective and/or prospective studies of VITT. The retrieved case reports and case series [6-9,22-41] comprised data of 74 VITT patients (22 males, 51 females, one unknown sex) with the age ranging from 18 to 77 years old, whereas the gathered retrospective and/or prospective studies [10,42-45] involved 376 VITT patients (144 males, 229 females, three unknown sex) with an age range from 18 to 79 years old. Among the total of 450 patients in the analysis, it can be observed that VITT cases were mainly female (n=280, 62%) and younger than 60 years old (>50%). The majority of VITT cases were associated with viral vector-based vaccines, particularly the AstraZeneca COVID-19 vaccine (n=429, 95%), followed by the Janssen COVID-19 vaccine (n=18, 4%), and to a much lower extent, mRNA-based vaccines, which are the Moderna COVID-19 vaccine (n=1, 0.2%) and the Pfizer COVID-19 vaccine (n=1, 0.2%). The range period between vaccination and symptom onset was between 1 and 48 days, with headache predominating the clinical presentation, with nearly all VITT patients reporting it as one of their first symptoms.

As displayed in Table 2, which comprised data from case

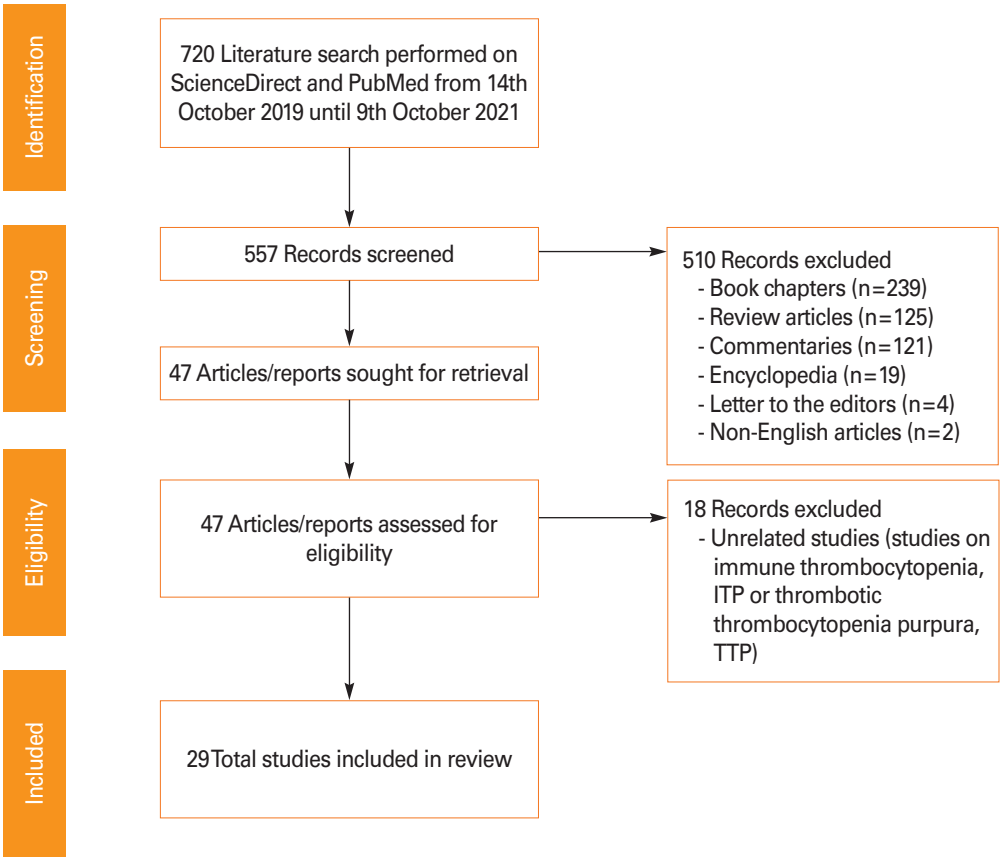


**Fig. 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

**Table 1.** Demographics, types of vaccine, clinical presentation, and laboratory finding of case report/series with VITT cases

| Author | Country | Study design | No. of patient | Age (yr) | Gender | Medical and medication history | Type of vaccine | Vaccination to symptom onset (day) | Clinical presentation | Laboratory finding | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | D dimer (ref <0.5 mg/L) | Platelet count (ref >150×10$^9$/L) | Anti-PF4 antibodies |
| Aladdin et al. [22] (2021) | Saudi Arabia | CR | 1 | 36 | F | Diabetes mellitus; oral antidiabetic | AZ | 14 | Sudden onset of focal left-sided convulsion, fever, vomiting, severe headache, tachycardia | >35 mg/L | 94×10$^9$/L | NA |
| Franchini et al. [28] (2021) | Italy | CR | 1 | 50 | M | NA | AZ | 7 | Headache | >10 mg/L | 15×10$^9$/L | Positive |
| Bjørnstad-Tuveng et al. [24] (2021) | Norway | CR | 1 | 30s | F | Mild preeclampsia at the end of pregnancy and treated with labetalol, uncomplicated childbirth with 1,500 mL of bleeding eleven months prior, for the past three months, had Duroferon for iron deficiency and desloratadine for allergies | AZ | 7 | Headache, lethargic, slurred speech, uncoordinated walking and movements | >7 mg/L | 37×10$^9$/L | Positive |
| Guan et al. [29] (2021) | Taiwan | CR | 1 | 52 | M | NA | AZ | 5 | Nausea, thunderclap headache, pain on left side of neck | >20 mg/L | 99×10$^9$/L | Positive |
| Clark et al. [26] (2021) | USA | CR | 1 | 40 | F | NA | JJ | 5 | Day 5: headache, sinus pressure, myalgia, sore throat with tonsillar exudate; day 12: worsening headache especially with movement, photophobia, intermittent dizziness | 27.15 mg/L | 20×10$^9$/L | Positive |
| Tølbøll Sørensen et al. [40] (2021) | Denmark | CR | 1 | 30 | F | Migraine; long-term use of third generation OCP | AZ | 8 | Malaise, persistent headache, ecchymosis | >20 mg/L | 57×10$^9$/L | Positive |
| Kennedy et al. [31] (2021) | USA | CR | 1 | 32 | M | NA | JJ | 8 | Worsening left leg pain, erythema, gravity-dependent venous distention | >14 mg/L | 43×10$^9$/L | Positive |
| Sangli et al. [37] (2021) | USA | CR | 1 | 65 | M | Chronic hypertension, hyperlipidemia | Moderna | 10 | 1 Week of bilateral lower extremity discomfort, intermittent headaches, 2 days of dyspnea | 1.98 mg/L | 14×10$^9$/L | Positive |
| Blauenfeldt et al. [9] (2021) | Denmark | CR | 1 | 60 | F | Hashimoto thyroiditis, hypertension; losartan, simvastatin, levothyroxine | AZ | 7 | Strong, persistent abdominal pain, left sided weakness and eye deviation to the right | 41.8 mg/L | 118×10$^9$/L | Positive |

(Continued on next page)

**Table 1.** Continued

| Author | Country | Study design | No. of patient | Age (yr) | Gender | Medical and medication history | Type of vaccine | Vaccination to symptom onset (day) | Clinical presentation | Laboratory finding | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | D dimer (ref <0.5 mg/L) | Platelet count (ref >150×10$^9$/L) | Anti-PF4 antibodies |
| Muir et al. [34] (2021) | USA | CR | 1 | 48 | F | Unremarkable | JJ | 14 | Malaise, abdominal pain | 117.5 mg/L | 13×10$^9$/L | Positive |
| Castelli et al. [25] (2021) | Italy | CR | 1 | 50 | M | NA | AZ | 12 | Severe headache, slight deviation of the right buccal rim, unstable walking, slight visual impairment | >10 mg/L | 20×10$^9$/L | NA |
| Rodriguez et al. [36] (2021) | Belgium | CR | 1 | 37 | F | NA | JJ | 7 | Headache, myalgia, fever, left leg pain, vomiting, right hemiplegia and hemineglect, left mydriasis | >35 mg/L | 50×10$^9$/L | Positive |
| Ramdeny et al. [35] (2021) | UK | CR | 1 | 54 | M | Rare congenital limb malformation (has strong family history of a rare congenital limb deformity) | AZ | 21 | Worsening headache, bruising, unilateral right calf swelling | 60 mg/L | 34×10$^9$/L | Positive |
| Suresh et al. [39] (2021) | UK | CR | 1 | 27 | M | NA | AZ | 48 hr | Intermittent headache, eye floaters, vomiting, left sided homonymous hemianopia | 34.071 mg/L | 90×10$^9$/L | Positive |
| Xie et al. [41] (2021) | UK | CR | 1 | 23 | NS | NA | NS | Within 1 week | Chest pain, breathlessness | 17.548 mg/L | 73×10$^9$/L | NA |
| Guetl et al. [30] (2021) | Austria | CR | 1 | 50 | F | Unremarkable | AZ | 10 | Severe back pain, severe headache | >33 mg/L | 27×10$^9$/L | Negative |
| Malik et al. [32] (2021) | USA | CR | 1 | 43 | F | History of dyslipidemia, anxiety depression, obstructive sleep apnea, GERD, obesity | JJ | 10 | Mild dyspnea, headache, fever, body aches, chills | 35.2 mg/L | 27×10$^9$/L | Positive |
| D'Agostino et al. [27] (2021) | Italy | CR | 1 | 54 | F | NA | AZ | 12 | Acute cerebrovascular accident | Elevated | Thrombocytopenia | NA |
| Greinacher et al. [8] (2021) | Germany & Austria | CS | 11 | 22–49 | 9 F, 2 M | 1 Had chronic neurologic disorder; 1 had type 1 Von Willebrand disease, factor V Leiden, anticardiolipin antibodies; 1 unknown; 8 NA | AZ | 5–16 | Fatigue, myalgia, headache, chills, fever, nausea, epigastric discomfort | 1.8–142 mg/L, 2 NA | 8–107×10$^9$/L, 1 NA | 9 Positive, 2 NA |
| Schultz et al. [6] (2021) | Norway | CS | 5 | 32–54 | 4 F, 1 M | 1 Had pollen allergy; contraceptive pills, pollen allergy; 1 had contraceptive vaginal ring; 1 had asthma, hypertension; 1 had HRT, antihypertensive agents, 1 none | AZ | 7–10 | Fever, headache, visual disturbances, drowsiness, back pain, abdominal pain, hemiparesis | 13–>35 mg/L | 10–70×10$^9$/L | All positive |

(Continued on next page)

**Table 1.** Continued

| Author | Country | Study design | No. of patient | Age (yr) | Gender | Medical and medication history | Type of vaccine | Vaccination to symptom onset (day) | Clinical presentation | Laboratory finding | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | D dimer (ref <0.5 mg/L) | Platelet count (ref >150×10$^9$/L) | Anti-PF4 antibodies |
| Scully et al. [7] (2021) | UK | CS | 23 | 21–77 | 14 F, 9 M | 1 Had history of DVT; 1 had combined OCP | AZ | 6–24 | Mild bruising and petechiae in some patients | >5–80 mg/L, 2 not done | 7–113×10$^9$/L, 1 Not done | 14 Positive, 1 negative, 8 not done |
| Mehta et al. [33] (2021) | UK | CS | 2 | 25 & 32 | M | 1 Had primary sclerosing cholangitis, migraines; ursodeoxycholic acid, budesonide, sumatriptan, amitriptyline | AZ | 6–9 | Thunderclap headache, meningitis headache, left hemiparesis, left-sided incoordination, left hemisensory loss, seizures, agitation, reduced GCS, decerebrate, photophobia, vomiting, petechial rash, gum bleeding | NA (because these cases are of the cases presented early during vaccination program. Hence, management of VITT not yet been established) | 19–30×10$^9$/L | 1 Positive, 1 test was not performed due to no samples available |
| See et al. [38] (2021) | USA | CS | 12 | 18–60 | F | 6 Had obesity, 1 had hypothyroidism; 1 had combined OCP | JJ | 6–15 | Headache, dizziness, neck pain, neck stiffness, lethargy, left-sided weakness, dry heaving, aphasia, chills, fever, nausea, vomiting, gaze deviation, blurry vision, left neglect, seizure, changes in speech, photophobia, cognitive fogginess, severe abdominal pain, bruising, unilateral leg swelling, loss of consciousness, dyspnea, petechial rash | 1.1–112.07 mg/L | 9–127×10$^9$/L | 11 Positive, 1 Not done |
| Bano et al. [23] (2021) | UK | CS | 3 | 53–61 | 2 F, 1 M | 1 Had asthma, hypertension, high BMI; currently on HRT and indapamide, 1 had fibromyalgia | AZ | 10–16 | Shortness of breath, pain and swelling in the right leg, headaches, facial weakness, hemiparesis, dysphasia, right arm weakness, discoordination | 5.63–47.88 mg/L | 21–25×10$^9$/L | All positive |

VITT, vaccine-induced immune thrombotic thrombocytopenia; Ref, reference; CR, case report; CS, case series; F, female; M, male; AZ, AstraZeneca vaccine; NA, not available; JJ, Janssen vaccine; OCP, oral contraceptive pill; GCS, Glasgow Coma Scale; NS, not stated; GERD, gastroesophageal reflux disease; HRT, hormone replacement therapy; DVT, deep vein thrombosis; BMI, body mass index.

**Table 2.** Imaging, types of VITT, other complications, and mortality of case report/series with VITT cases

| Author | Radiological imaging | Type of VITT | | | | | | | Other complications | Outcomes (died/alive) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Aladdin et al. [22] (2021) | Brain CT: superior sagittal thrombosis; CTV: extensive dural venous sinus thrombosis; CT abdomen & pelvis: extensive portal vein thrombosis, superior mesenteric vein thrombosis, potential splenic and hepatic infarction | | | | | | | | DIC | Died |
| Franchini et al. [28] (2021) | Brain CT: hemorrhage in the left cerebral hemisphere; CTA intracranial circle vessels: multiple small bleeding spots in the context of the left parenchymal hemorrhage | | | | | | | | ICH | Died |
| Bjørnstad-Tuveng et al. [24] (2021) | CT head: large intracerebral hemorrhage; postmortem examination: fresh small thrombi found in the transverse sinus, frontal lobe and pulmonary artery | | | | | | | | ICH | Died |
| Guan et al. [29] (2021) | CTV: filling defect in the left jugular vein, filling defect in confluence of the sinus and represent the lack of contrast medium in the left transverse sinus | | | | | | | | | Alive |
| Clark et al. [26] (2021) | CT: CVST involving the left transverse and sigmoid sinuses, extending into the left internal jugular vein, with acute subsegmental pulmonary emboli | | | | | | | IJVT | | Alive |
| Tølbøll Sørensen et al. [40] (2021) | Duplex ultrasonography abdomen & confirmatory CTA abdominal: portal vein thrombosis; cerebral CTV: newly developed CVST | | | | | | | | | Alive |
| Kennedy et al. [31] (2021) | Lower extremity ultrasound: nonocclusive thrombi in the left distal popliteal vein and peroneal vein | | | | | | | | | Alive |
| Sangli et al. [37] (2021) | CTA chest: large, bilateral, acute PE with right ventricular strain; Doppler lower extremities: acute DVT in both lower extremities; CTA head and neck: CVST, which was confirmed with a CTV | | | | | | | | | Died |
| Blauenfeldt et al. [9] (2021) | CT of the abdomen: bilateral adrenal hemorrhages and subcapsular renal hematoma; MRI angiography: occlusion of the right ICA | | | | | | | | Adrenal hemorrhages | Died |
| Muir et al. [34] (2021) | CT abdomen and pelvis: extensive SVT; Head CT: CVST involving the right transverse and straight sinuses; brain MRI and MRV: progressive thrombosis with hemorrhagic stroke evident; repeat CTA: new thrombus involving the right hepatic and splenic veins | | | | | | | | DIC, ICH | Alive |
| Castelli et al. [25] (2021) | Brain CT scan: intra-parenchymal hemorrhage in the left hemisphere; CTA: multiple bleeding spots within the parenchymal hemorrhage | | | | | | | | Intraparenchymal hemorrhage | Died |

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**Table 2.** Continued

| Author | Radiological imaging | Type of VITT | | | | | | | Other complications | Outcomes (died/alive) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Rodriguez et al. [36] (2021) | CT scan: multiple bilateral intraparenchymal hemorrhagic areas; MRI: thrombosis of the major anterior part of the sagittal superior sinus with bilateral intraparenchymal hemorrhagic complications; Doppler ultrasound: left popliteal vein thrombosis | | | | | | | | Intraparenchymal hemorrhage, diabetes insipidus | Died |
| Ramdeny et al. [35] (2021) | CT: extensive CVST; ultrasonography: concurrent venous thrombosis in the portal vein | | | | | | | | Thrombophlebitis of the right leg | Alive |
| Suresh et al. [39] (2021) | CTV: significant CVST; Repeat CT head: acute parenchymal bleed with subdural extension | | | | | | | | ICH | Died |
| Xie et al. [41] (2021) | CTPA: PE; repeat CT: RV thrombus, splenic vein thrombus and bilateral adrenal hemorrhage; MRI: embolic infarcts or posterior reversible encephalopathy syndrome | | | | | | | RV thrombus | Adrenal hemorrhages | Alive |
| Guetl et al. [30] (2021) | Contrast-enhanced MRI: multifocal thrombus formation in the pelvic region; CTPA: subsegmental embolus in the posterior-basal right lower lobe | | | | | | | Multifocal thrombus formation in the pelvic region | | Alive |
| Malik et al. [32] (2021) | CTPA: PE at right upper lobe, right lower lobe, left lower lobe lobar, segmental PE; CTA of head & neck: non-occlusive right ICA thrombus in the right carotid bulb/proximal right ICA | | | | | | | | | Alive |
| D'Agostino et al.[27] (2021) | CT scan: multiple subacute intra-axial hemorrhages in atypical locations, including right frontal and the temporal lobes; CTA: partial thrombosis of the vein of Galen, floating thrombus within the aortic arch; MRI: acute basilar thrombosis associated with the superior sagittal sinus thrombosis | | | | | | | Aortic arch thrombus | DIC, ICH, adrenal hemorrhage | Died |
| Greinacher et al. [8] (2021) | 1 CT: portal vein thrombosis and peripheral PE. Repeat CT imaging: progression of portal-vein thrombosis to include the splenic and upper mesenteric veins. In addition, small thrombi were visualized in the infrarenal aorta and both iliac arteries; 10 not stated | (9) | MV (3), PV (3), SV (3), HV (3) | | | (3) | | 1 Aortoiliac thrombosis, 1 right intraventricular, iliofemoral vein and IVC thrombus, 1 widespread macrovascular thrombus (brain, lung, kidney), 1 multiple organ thrombi | 1 ICH | 4 Alive, 6 died, 1 unknown |

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**Table 2.** Continued

| Author | Radiological imaging | Type of VITT | | | | | | | Other complications | Outcomes (died/alive) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Schultz et al. [6] (2021) | 1 Head CT: thrombosis in the left transverse and sigmoid sinuses. New CT scan: massive cerebellar hemorrhage and edema in the posterior fossa; 1 CTV: venous thrombosis with occlusion of the transverse and sigmoid sinuses and hemorrhagic infarction in the left hemisphere; 1 thoracoabdominal CT scan: thrombosis of several branches of the portal vein with occlusion of the left intrahepatic portal vein and left hepatic vein. In addition, thrombosis was observed in the splenic vein, the azygos vein, and the hemiazygos vein; 1 cerebral CT with venography: massive thrombosis in the deep and superficial cerebral veins and right cerebellar hemorrhagic infarction; 1 head CT: right frontal hemorrhage. CT scan with venography: massive cerebral vein thrombosis with global edema and growth of hematoma | (4) | PV (1), SV (1), HV (1) | | | | | 1 Azygos vein, hemiazygos vein, basivertebral veins thrombus | 2 ICH, 2 hemorrhagic infarctions | 2 Alive, 3 died |
| Scully et al. [7] (2021) | Not stated | (13) | PV (3) | (1) | (2) | (5) | (2) | 1 Ischemic bowel with infarction, 1 aortic thrombosis, 1 lung and intestine thrombosis, 1 IJVT | 4 ICH, 1 adrenal hemorrhage, 1 hemorrhagic symptom only | 16 Alive, 7 died |
| Mehta et al. [33] (2021) | 1 Neuroimaging: superior sagittal sinus, cortical vein thrombosis and significant cortical oedema with small areas of parenchymal and subarachnoid hemorrhage; 1 neuroimaging: superior sagittal sinus thrombosis with extension into the cortical veins, and hemorrhage in lobar and subarachnoid locations. Repeat neuroimaging: extensive bilateral frontoparietal intraparenchymal and subarachnoid hemorrhages with midline shift | (2) | | | | | | | 2 ICH | 2 Died |

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**Table 2.** Continued

| Author | Radiological imaging | Type of VITT | | | | | | | Other complications | Outcomes (died/alive) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| See et al. [38] (2021) | 1 Head CT: large right temporoparietal hemorrhage. CTA of the head and neck: right transverse and sigmoid sinus thromboses; 1 head CT: a left temporal lobe hemorrhage and suspected underlying sinus thrombosis. CTV: thromboses in the straight sinus, confluence of sinuses, left transverse sinus, left sigmoid sinus, and left intracranial internal jugular vein; 1 CTA of the head and neck, MRI and venogram of the brain: right frontal lobe hemorrhage, possible right subarachnoid hemorrhage, and right superior sagittal sinus vein thrombosis; 1 ultrasound of the abdomen: portal vein thrombosis. CTA of the chest: right PE. MRV: right transverse and sigmoid sinus thrombosis; 1 ultrasound: right lower extremity DVT. MRI of the brain: right transverse sinus venous thrombosis and right internal jugular vein thrombosis; 1 ultrasound of the abdomen: portal vein thrombosis with mild retroperitoneal, intraperitoneal, and pelvic hemorrhage. Lower extremity ultrasound: DVT of the right posterior tibial and peroneal veins. Head CT: thrombosis of the right transverse sinus and straight sinus and ICH; 6 not stated | (12) | MV (1), PV (2), SV (1), HV (1) | | (3) | (3) | | 5 IJVT | 7 ICH | 9 Alive, 3 died |
| Bano et al. [23] (2021) | 1 CTPA: acute thrombus as filling defect (arrow) involving the right pulmonary artery branch extending into the right inferior pulmonary artery and segmental branches; 1 head CT: extensive intracerebral hemorrhage. CTV: confirmed CVST; 1 head CT: extensive CVST with the extension of thrombus into the left internal jugular vein and secondary subarachnoid hemorrhage | (2) | | | | (1) | | 1 IJVT | 2 ICH | 1 Alive, 2 died |

VITT, vaccine-induced immune thrombotic thrombocytopenia; CVST, cerebral venous sinus thrombosis; SVT, splanchnic vein thrombosis; MI, myocardial infarctions; DVT, deep vein thrombosis; PE, pulmonary embolism; IS, ischemic stroke; CT, computed tomography; CTV, CT venography; DIC, disseminated intravascular coagulation; CTA, CT angiography; ICH, intracerebral hemorrhage; IJVT, internal jugular vein thrombosis; MRI, magnetic resonance imaging; ICA, internal carotid artery; MRV, magnetic resonance venography; CTPA, CT pulmonary angiogram; RV, right ventricle; IVC, inferior vena cava; MV, mesenteric vein; PV, portal vein; SV, splenic vein; HV, hepatic vein.

**Table 3.** Demographics, types of vaccine, clinical presentation and laboratory finding of retrospective and/or prospective studies reporting VITT cases

| Author | Country | Study design | Mean FU/ duration of study/ duration of data collection | No. of patient | Age (yr) | Gender | Medical & medication history | Type of vaccine | Vaccination to symptom onset (day) | Clinical presentation | Laboratory finding | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | D dimer (ref <0.5 mg/L) | Platelet Count (ref >150×10$^9$/L) | Anti-PF4 antibodies |
| Wolf et al. [45] (2021) | Germany | Retrospective study | NA | 3 | 22–46 | F | NA | 3 AZ | 4–8 | Shivering, fever, headache, mild aphasia, homonymous hemianopia to the right, reduced consciousness, generalized epileptic seizures | 2.12–22.8 mg/L | 60–92×10$^9$/L | All positive |
| Tiede et al. [44] (2021) | Germany | Single center retrospective cohort study | March 8 until April 4, 2021 | 5 | 41–67 | F | NA | 5 AZ | 5–11 | Headache, fatigue, dysarthria, somnolence, dysphasia, diplopia, right-sided hemiparesis, conjugated gaze palsy and arterial hypertension | 22.4–>35.2 mg/L | 12–105×10$^9$/L | All positive |
| Perry et al. [42] (2021) | UK | Prospective and retrospective multicenter cohort study | April 1 until May 20, 2021 | 70 | 32–55 | 39 F, 31 M | NA | AZ | 7–12 | One patient developed clumsiness of the left arm 40 days after first dose of AZ vaccine | 62/70 (89%) have high D-dimer | All 70 patients (100%) have low blood platelet count | 56/58 positive |
| Pavord et al. [10] (2021) | UK | Prospective and retrospective cohort study | March 22 until June 6, 2021 | 220 (170 definite, 50 probable) | 18–79 | 119 F, 98 M, 3 not stated | 97/165 (59%) have a past or current medical illness | AZ | 5–48 | NA | 5–80 mg/L | 218/220 (99%) had thrombocytopenia | 198/220 (90%) positive, 6/220 (2.7%) negative, 16/220 (7.3%) not performed ELISA testing |
| Sánchez van Kammen et al. [42] (2021) | Netherlands | Prospective and retrospective cohort study | March 29 until June 18, 2021 | 78 | 45 (mean) | 63 F, 15 M | 19/78 (24%) had conventional CVST risk factor, 11/63 (17%) use oral contraceptives, 2/63 (3%) had hormone therapy, 5/78 (6%) had infection, 1/78 (1%) had previous thromboembolism which is DVT, 1/78 (1%) had known thrombophilia, 3/78 (4%) had cancer | 76 AZ, 1 JJ, 1 Pfizer | 7–10 (IQR) | 75/78 (96%) presented with headache, 41/78 (53%) with focal neurologic deficits, 8/78 (10%) with seizures, 18/75 (24%) coma, 7/78 (9%) with petechiae, 2/78 (3%) with purpura, 4/78 (5%) with mucosal bleeding | Not available because the authors follow Brighton Collaboration guidelines | 25–71×10$^9$/L | 63/69 (91%) positive |

Values are presented as mean, median, or range, unless otherwise stated.
VITT, vaccine-induced immune thrombotic thrombocytopenia; FU, follow-up; Ref, reference; NA, not available; F, female; M, male; AZ, AstraZeneca vaccine; ELISA, enzyme-linked immunoassay; CVST, cerebral sinus venous thrombosis; DVT, deep vein thrombosis; JJ, Janssen vaccine; IQR, interquartile range.

**Table 4.** Imaging, types of VITT, other complications and mortality in retrospective/prospective studies with VITT cases

| Author | Radiological imaging | Type of VITT | | | | | | | Other complications | Outcomes (died/alive) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Wolf et al. [45] (2021) | 1 MRI: blood in the subarachnoid space adjacent to the falx cerebri on both sides. The superior sagittal sinus, the left-hand transverse sinus, and the sigmoid sinus were thrombosed; DSA: confirmed the occlusion of the ascending cerebral veins and the said sinuses. 1 MRI: a thrombotic occlusion of the superior sagittal sinus and the left-hand transverse sinus and sigmoid sinus; DSA: the occlusion of the superior sagittal sinus and the left transverse sinus and the sigmoid sinus. 1 MRI: a thrombotic occlusion of the straight sinus and a non-occlusive thrombus in the superior sagittal sinus; DSA: the occlusion of the straight sinus and a non-occlusive thrombus of the superior sagittal sinus | (3) | | | | | | | | All alive |
| Tiede et al. [44] (2021) | 1 Imaging: left transverse and sigmoid sinus thrombosis, left temporal bleeding. 1 Imaging: cortical infarctions and aortic arch thrombi. 1 Imaging: SVT day 6 after admission. 1 Imaging: right ICA and middle cerebral artery (M1) thrombosis. Right MCA territory infarction with hemorrhagic transformation. 1: No pathology | (1) | MV (1), PV (1), SV (1), HV (1) | | (1) | | (3) | 1 TMA, 1 aortic arch thrombus, 1 popliteal artery thrombosis | 1 ICH | All alive |
| Sánchez van Kammen et al. [43] (2021) | CVST confirmed with CTV, MRI, MRV, catheter angiography or autopsy | 78/78 (100%) | 10/70 (14%) | 2/70 (3%) | 6/70 (9%) | 16/70 (23%) | | 6/70 (8%) pelvic vein thrombosis, 25/70 (36%) thromboembolism +CVST, 1/70 (1%) kidney thrombosis, 3/70 (4%) IVC thrombus,1/70 (1%) aortic arch thrombus, 1/70 (1%) ventricular thrombus, 1/70 (1%) basilar artery | 53/78 (68%) ICH, 4/75 (5%) had focal edema only | 36/76 (47%) Died |
| Pavord et al. [10] (2021) | For patients who presented with headaches, CT imaging/MRI were used | 110/220 (50%) | 41/220 (19%); 30 PVT, 22 other SVT, 11 had both | 9/220 (4%) | 82/220 (37%) (40 DVT, 63 PE, 21 had both) | | 26/220 (12%) had aortic thrombosis or ischemic limb | 36% of CVST patient had ICH | 170/219 (78%) Alive, 49/219 (22%) died, 1 patient unknown outcome | |

(Continued on next page)

**Table 4.** Continued

| Author | Radiological imaging | Type of VITT | | | | | | | Other complications | Outcomes (died/alive) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Perry et al. [42] (2021) | CTV: CVST in all 70 patients | 70/70 (100%) | 31/70 (44%) had evidence of extracranial venous thrombosis, arterial thrombosis, or both, with PE and hepatic portal vein thrombosis being particularly common | | | | | | | 29% Died |

VITT, vaccine-induced immune thrombotic thrombocytopenia; CVST, cerebral venous sinus thrombosis; SVT, splanchnic vein thrombosis; MI, myocardial infarctions; DVT, deep vein thrombosis; PE, pulmonary embolism; IS, ischemic stroke; MRI, magnetic resonance imaging; DSA, digital subtraction angiography; ICA, internal carotid artery; MCA, middle cerebral artery; MV, mesenteric vein; PV, portal vein; SV, splenic vein; HV, hepatic vein; TMA, thrombotic microangiopathy; ICH, intracerebral hemorrhage; CTV, CT venography; CT, computed tomography; PVT, portal vein thrombosis; MRV, magnetic resonance venography; IVC, inferior vena cava.

series and case reports, CVST is the most severe manifestation of VITT with 55 cases reported among the total of 24 studies, followed by PE (n=17), SVT (n=14), DVT (n=8), ischemic stroke (n=4), and myocardial infarction (MI) (n=1). Twenty-five of the 74 VITT cases are complicated by the concurrent presence of a life-threatening type of stroke, which is intracerebral hemorrhage (ICH). In addition to CVST, some patients (n=24) had concomitant thromboses at different sites.

Table 4 presents data from retrospective and/or prospective studies. All VITT patients (n=3) from the study by Wolf et al. [45] had CVST. Tiede et al. [44] reported on five VITT patients: one had CVST accompanied by the presence of thrombotic microangiopathy and left temporal bleeding, one patient had SVT, and three patients had had an ischemic stroke with two of them having concomitant thrombosis at other sites (aortic arch and popliteal artery). Perry et al. [42] outlined 70 VITT patients, all of whom had CVST, and 31 of whom also had extracranial venous thrombosis, arterial thrombosis, or both, with PE, hepatic vein thrombosis and portal vein thrombosis being the most prevalent manifestations. Pavord et al. [10] described 220 VITT patients that consisted of 170 definite and 50 probable cases. Among these patients, the most prevalent presenting feature of VITT was CVST (n=110), followed by PE (n=63), SVT (n=41), DVT (n=40), aortic thrombosis or ischemic limb (n=26), and MI (n=9). The occurrence of ICH was observed in 40 out of 110 CVST patients. Sánchez van Kammen et al. [43] reported on 78 VITT patients. All the patients had CVST, and 70 of them had concomitant thrombotic events including PE (n=16), SVT (n=10), DVT (n=6), MI (n=2), and other less common types of thrombosis such as pelvic vein thrombosis, kidney thrombosis, inferior vena cava thrombosis, aortic arch thrombus, ventricular thrombus, and basilar artery thrombus. The occurrence of ICH was seen in 94 of the 110 CVST patients. From the presented studies, 137 patients died, constituting 30% of the overall patient population, while 309 patients (69%) survived from this condition and the status of the remaining four patients is unknown.

For the laboratory findings of these VITT patients, a low blood platelet count (reference range, $>150\times10^9$/L) and D-dimer elevation (reference range, <0.5 mg/L) was seen in the majority of studies in which 99% (n=446) had thrombocytopenia and 79% (n=356) had markedly high D-dimer levels. PF4 ELISA results were positive in nearly all cases (85%, n=381), with optical density readings typically exceeding 0.5.

As illustrated in Table 5, 24 of 26 retrieved studies employed various types of anticoagulation in treating the thrombosis in

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**Table 5.** Management of VITT patients

| Author | Country | Type of VITT | | | | | | | Other complications | Management |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Aladdin et al. [22] (2021) | Saudi Arabia | | | | | | | | DIC | Enoxaparin (stop due to DIC), blood transfusion |
| Franchini et al. [28] (2021) | Italy | | | | | | | | ICH | 9 RBC units; 4 platelets apheresis unit, infusion of fibrinogen concentrate, neurosurgery |
| Guan et al. [29] (2021) | Taiwan | | | | | | | | | IVIG 1 mg/kg for 2 days, apixaban |
| Tølbøll Sørensen et al. [40] (2021) | Denmark | | | | | | | | | Tinzaparin 4,500 IU OD, fibrinogen substitution tinzaparin replaced with fondaparinux 7.5 mg OD after suspected aHIT. Upon discharge, rivaroxaban was prescribed |
| Kennedy et al. [31] (2021) | USA | | | | | | | | | 1 g/kg of IVIG daily for 2 days, 1 mg/kg of prednisone, argatroban. Transitioned from argatroban to apixaban |
| Sangli et al. [37] (2021) | USA | | | | | | | | | 2 Doses of IVIG & 40 mg of IV dexamethasone for 4 days, unfractionated heparin therapy after platelet transfusions (3 days later, heparin was withdrawn), 0.02 mg/kg/hr of bivalirudin treatment & plasmapheresis |
| Blauenfeldt et al. [9] (2021) | Denmark | | | | | | | | Adrenal hemorrhages | Hydrocortisone 100 mg TID, three pools of platelet concentrate before hemicraniectomy, seven pools of platelet concentrates. Postoperative dalteparin 5,000 IU OD |
| Muir et al. [34] (2021) | USA | | | | | | | | DIC, ICH | Initially, unfractionated heparin was administered. Heparin was switched to argatroban, IVIG at a dose of 1 g/kg of ideal body weight for 2 days |
| Castelli et al. [25] (2021) | Italy | | | | | | | | Intraparenchymal hemorrhage | Fibrinogen concentrate (10 g total), platelet (4-unit total), bilateral decompressive craniectomy |
| Rodriguez et al. [36] (2021) | Belgium | | | | | | | | Intraparenchymal hemorrhage, diabetes insipidus | Subcutaneous tinzaparin 10.000 U/day and elastic compression stocking, IVIG 1 g/kg/day, IV danaparoid sodium, 40 mg of IV dexamethasone. Platelet transfusion before an external ventricular shunt and intracranial pressure monitoring implementation |
| Ramdeny et al. [35] (2021) | UK | | | | | | | | Thrombophlebitis of the right leg | IVIG and danaparoid |

(Continued on next page)

**Table 5.** Continued

| Author | Country | Type of VITT | | | | | | | Other complications | Management |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Suresh et al. [39] (2021) | UK | | | | | | | | ICH | IVIG 1 g/kg OD, dabigatran, idarucizumab, prednisolone 80 mg OD (1 mg/kg) |
| Xie et al. [41] (2021) | UK | | | | | | | RV thrombus | Adrenal hemorrhages | Apixaban, plasma exchange, IV methylprednisolone and heparin infusion |
| Guetl et al. [30] (2021) | Austria | | | | | | | Multifocal thrombus formation in the pelvic region | | High dose of IVIG, dexamethasone 40 mg orally, IV argatroban at a dose of 2 μg/kg/min, oral dabigatraban 150 mg BID (after 4 days with IV argatroban) |
| Malik et al. [32] (2021) | USA | | | | | | | | | 60 g IVIG, 7.5 g fondaparinux SC daily, apixaban 5 mg orally BID |
| Greinacher et al. [8] (2021) | Germany & Austria | (9) | MV (3), PV (3), SV (3), HV (3) | | | (3) | | 1 Aortoiliac thrombosis, 1 right intraventricular, iliofemoral vein and IVC thrombus, 1 widespread macrovascular thrombus (brain, lung, kidney), 1 multiple organ thrombi | 1 ICH, 1 gastrointestinal bleeding | Enoxaparin (2), heparin (4), apixaban (1), platelet concentrate (1), red cell (1), prothrombin complex concentrates (1), recombinant factor VIIa (1); treatment was not mentioned for 6 patients |
| Schultz et al. [6] (2021) | Norway | (4) | PV (1), SV (1), HV (1) | | | | | 1 Azygos vein, hemiazygos vein, basivertebral veins thrombus | 2 ICH, 2 hemorrhagic infarctions | Heparin (1), warfarin (2), LMWH (4), IVIG (4), corticosteroids (4), platelet transfusion (4), neurosurgery (3), endovascular intervention with thrombectomy (1) |
| Mehta et al. [33] (2021) | UK | (2) | | | | | | | 2 ICH | Unfractionated heparin (1), dexamethasone 40 mg OD (1), IVIG 1 g/kg (1), platelet transfusion (1); treatment was not mentioned for 1 patient |
| See et al. [38] (2021) | USA | (12) | MV (1), PV (2), SV (1), HV (1) | | (3) | (3) | | 5 IJVT | 7 ICH | Heparin (6), non-heparin anticoagulant (10), IVIG (7), systemic corticosteroid (3), platelet transfusion (4) |
| Bano et al. [23] (2021) | UK | (2) | | | | (1) | | 1 IJVT | 2 ICH | LMWH (1), fondaparinux (1), argatroban (1), platelet transfusion (3), cryoprecipitate transfusion (1), IVIG 1 g/kg (1), corticosteroid 20 mg (2), neurosurgical (2) |
| Tiede et al. [44] (2021) | Germany | (1) | MV (1), PV (1), SV (1), HV (1) | | (1) | | (3) | 1 TMA, 1 aortic arch thrombus | Left temporal bleeding | Heparin (1), argatroban (4), alteplase (1), IVIG 1 g/kg for 2 days (3), dexamethasone (3), eculizumab 900 mg weekly (2) |

(Continued on next page)

**Table 5.** Continued

| Author | Country | Type of VITT | | | | | | | Other complications | Management |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Sánchez van Kammen et al. [43] (2021) | Netherlands | 78/78 (100%) | 10/70 (14%) | 2/70 (3%) | 6/70 (9%) | 16/70 (23%) | | 6/70 (8%) pelvic vein thrombosis, 25/70 (36%) concomitant thromboembolism +CVST, 1/70 (1%) kidney thrombosis, 3/70 (4%) IVC thrombus, 1/70 (1%) aortic arch thrombus, 1/70 (1%) ventricular thrombus, 1/70 (1%) basilar artery | 53/78 (68%) ICH, 4/75 (5%) had focal edema only | CVST treatment: anticoagulant treatment; heparin (30), non-heparin anticoagulants (37), endovascular treatment (16), decompressive hemicraniectomy (23), intensive care unit (60); immunomodulation treatment: any immunomodulation therapy (52), IVIG (47), plasma exchange (6), corticosteroids (25), eculizumab (2), rituximab (1), platelet transfusion (20) |
| Pavord et al. [10] (2021) | UK | 110/220 (50%) | 41/220 (19%); 30 PVT, 22 other SVT, 11 had both | 9/220 (4%) | 82/220 (37%); 40 DVT, 63 PE, 21 had both | | | 26/220 (12%) had aortic thrombosis or ischemic limb | 36% of CVST patient had ICH | IVIG 1 g/kg on day 1 of admission: In 11%, second dose was given for ongoing or relapse disease; plasma exchange: 17 patients with severe disease involving CVST, thrombosis at multiple sites or both; IV methylprednisolone, oral/IV dexamethasone, oral prednisolone: 57 patients and in 50% of those with a platelet count <30 000/mm$^3$; neurosurgery/thrombectomy: 33 patients with extensive CVST with or without secondary ICH, anticoagulation; 68% non-heparin-based anticoagulation (argatroban, fondaparinux, apixaban, dabigatran), 23% heparin: 200 patients |

(Continued on next page)

**Table 5.** Continued

| Author | Country | Type of VITT | | | | | | | Other complications | Management |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CVST | SVT | MI | DVT | PE | IS | Others | | |
| Perry et al. [42] (2021) | UK | 70/70 (100%) | 31/70 (44%) had evidence of extracranial venousthrombosis, arterial thrombosis, or both, with PE and hepatic portal vein thrombosis being particularly common | | | | | | | Pharmacological: anticoagulant (60), LMWH/heparin (16), non-heparin parenteral anticoagulant (50), direct oral anticoagulant (22), corticosteroid (51), fibrinogen replacement (15), IVIG (55), plasma exchange (16), platelet transfusion (25); invasive: endovascular management (9), intracranial pressure monitor (13), decompressive hemicraniectomy (13) |

VITT, vaccine-induced immune thrombotic thrombocytopenia; CVST, cerebral venous sinus thrombosis; SVT, splanchnic vein thrombosis; MI, myocardial infarctions; DVT, deep vein thrombosis; PE, pulmonary embolism; IS, ischemic stroke; DIC, disseminated intravascular coagulation; ICH, intracerebral hemorrhage; RBC, red blood cell; IVIG, intravenous immunoglobulin; OD, optical density; aHIT, autoimmune heparin-induced thrombocytopenia; TID, 3 times a day; ICH, intracerebral hemorrhage; RV, right ventricle; BID, 2 times a day; SC, subcutaneous; MV, mesenteric vein; PV, portal vein; SV, splenic vein; HV, hepatic vein; IVC, inferior vena cava; LMWH, low molecular weight heparin; IJVT, internal jugular vein thrombosis; TMA, thrombotic microangiopathy; PVT, portal vein thrombosis; IVC, inferior vena cava.

VITT patients [6,8-10,23,25,26,29-45]. These include enoxaparin, apixaban, bivalirudin, tinzaparin, argatroban, dalteparin, danaparoid sodium, dabigatran, fondaparinux, rivaxoraban, and heparin. In a study by Tiede et al. [44], a thrombolytic agent, altelapse, was used in addition to anticoagulation treatment. As seen in 18 studies, IVIG was administered to VITT patients as the initial treatment for managing the immune response [6,10, 23,26,29-39,42-44]. Besides IVIG, 16 studies reported the use of another class of drug, a steroid, as the second line treatment of these immune-mediated disorders [6,9,10,23,26,30,31,33,36-39, 41-44]. Monoclonal antibodies including eculizumab and rituximab were also administered as a second line immunomodulation treatment of VITT, as reported in two studies [43,44]. Five studies employed plasma exchange as a salvage therapy for patients [10,37,41-43], particularly in patients with poor prognosis [41], with a thrombosis that had progressed [37] or in patients with severe disease involving CVST, multiple site thrombosis, or both [10]. In some studies, platelet transfusions, cryoprecipitate transfusions, or fibrinogen concentrate were administered to patients who particularly suffered from massive bleeding or before neurosurgical intervention [6,8,9,23,25,28,33,\36-38,40,42, 43]. In a case series involving three VITT patients, one of them was transfused with platelets and cryoprecipitate to maintain the blood platelet count above $50\times10^9$/L [23]. Three studies reported administering red blood cell or blood transfusion to their patients [8,22,28]. In a case series by Greinacher et al. [8], one patient was administered with the recombinant factor VIIa after the repeat CT imaging revealed diffused gastrointestinal bleeding. Along with the pharmacological treatment, VITT patients in 11 studies underwent invasive treatment such as neurosurgery, decompressive craniectomy, external ventricular shunt, intracranial bolt insertion, and endovascular thrombectomy in order to monitor and manage the pressure that had built up within their cranium, which is typically caused by hemorrhages [6,9,10, 23,25,28,36,39,42,43,45]. In a case study by Rodriguez et al. [36], elastic compression stockings were used as a non-pharmacological treatment for the symptoms of DVT.

## Discussion

### Prevalence

VITT is a rare but serious adverse event following adenoviral vector-based vaccinations for COVID-19. Findings showed that VITT is a rare sequel that is almost exclusively seen with replication defective viral vector-based vaccines, which are the AstraZeneca COVID-19 vaccine (95%) and the Janssen

COVID-19 vaccine (4%), with much rarer reports (0.4%) involving mRNA-based vaccines such as the Moderna COVID-19 vaccine and the Pfizer COVID-19 vaccine.

### Mechanism of action

Even though the exact mechanism by which this condition occurs is not concretely understood, some authors have hypothesized that adenoviral DNA or other currently unknown negatively charged (polyanionic) vaccine components could bind to positively charged (polycationic) PF4 due to electrostatic interaction, causing conformational changes and then forming a neoantigen that further triggers the production of an anti-PF4 antibody [2,46-48]. The anti-PF4 antibody recognizes the neoantigen, leading to cross-linking between their Fc region and the low affinity Fc receptor IIA (FcRIIa) presented on the surface of platelets, resulting in the formation of pathogenic immunocomplexes [46]. These complexes stimulate platelet activation [46], causing degranulation, enabling PF4 to be liberated from the alpha granule [48,49]. Concurrently, platelet activation also promotes the release of prothrombotic platelet-derived microparticles, which contribute to the formation of clots and the induction of a prothrombotic cascade [49]. Not only that, but the interaction of PF4, activated platelets and antibodies stimulates the release of neutrophil extracellular traps from leukocytes, hence increasing the likelihood of thrombotic events [48,49]. As a result of this consumptive process, the platelets are used up, thereby decreasing the platelet count and ultimately causing thrombocytopenia [50]. Additionally, the reticuloendothelial system, specifically the spleen, eliminates immunoglobulin G-coated platelets, intensifying thrombocytopenia [33,51].

### Types of VITT

A total of 317 out of 450 VITT patients presented with thrombosis at an atypical site, which is the cerebral venous sinus—and therefore known as CVST—, making it the most dominant manifestation of VITT. Even so, the development of thrombosis at the typical sites are also common, for instance PE and DVT which account for more than 151 cases. PE and DVT as well as CVST are types of venous thromboembolism (VTE). DVT is characterized by the formation of a blood clot in a deep vein, typically in the lower leg, thigh, or pelvis, and in rare cases in the arm [52]. DVT can be proximal (popliteal, femoral, or iliac veins) or distal (internal jugular, subclavian, axillary, and brachial veins) and embolization is a concern with proximal DVTs [53,54]. PE is not a disease, but rather a serious complication of underlying venous thrombosis, which usually results from a thrombus originating in the deep veins of the lower extremities that travels to the lungs, thereby causing blockage [55]. SVT, which accounts for over 66 cases, is an unusual manifestation of VTE and another uncommon anatomical site of thrombosis. SVT encompass splenic vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, and hepatic vein thrombosis (portal vein thrombosis being the most prevalent form of SVT). In addition to VTE, arterial thromboembolism events such as MI and ischemic stroke occur to a lesser extent among VITT patients with 12 cases and seven cases, respectively.

The majority of the presented CVST-associated VITT cases (n=119) are complicated by the occurrence of a hemorrhagic stroke, which is an ICH. This combination represents the most serious form of venous sinus thrombosis and is usually associated with worse outcomes such as death. Pathogenesis of CVST comprises two mechanisms: firstly, thrombosis in the venous sinus of the brain can cause focal neurological symptoms [56] including hemiparesis [6,23,33], aphasia [38], slurred speech [24,38], hemiplegia [36], eye deviation [9], and hemianopia [39]. Secondly, thrombosis at this site can obstruct venous drainage, leading to venous congestion that further causes an increase in the venous and capillary pressure [56-58]. If the arterial pressure is unable to counter the venous pressure, cerebral edema, hemorrhage, or ischemia occur [56-58]. These two processes can happen concurrently [56].

### Signs and symptoms

Presenting signs and symptoms of the VITT patients reflect the underlying location of the thrombosis. From the gathered studies, VITT patients with SVT experience fever, vomiting, abdominal pain, and back pain, while patients with DVT encounter lower extremity discomfort, leg pain, and venous distention. On the other hand, patients that have chest pain, breathlessness, and dyspnea are suggestive of having PE. For CVST, even though its symptoms are diverse and myriad, the most frequent one is a headache, which is diffuse and may progress over days to weeks. A headache may be the sole complaint or associated with other focal neurological symptoms. The signs and symptoms of ischemic stroke and MI are more or less identical to CVST and PE, respectively, since the thrombosis occurs at the same location, which is at the venous or arterial vessels of the brain or heart. For MI, the most common sign and symptom that can be observed is chest pain. In some cases, multiple locations of symptoms occur simultaneously, indicating the occurrence of thrombosis at multiple sites.

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### Risk factor

Although VITT cases are not age- or gender-specific, it can be noted from the retrieved studies that persons younger than 60 years old (>50%) and females were mostly affected by this clinical syndrome, representing 62% of the total patients. However, a review by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) stated that the higher rates of VITT cases among females is not seen across all age groups and the differences remain small [3].

Besides, according to the findings, a great majority of patients were previously healthy and fit with no remarkable medical or medication history. The use of the contraceptive pill, hormone replacement therapy, a history of thromboembolism, obesity, and hypertension are the most significant potential predisposing factors that can be observed among them. Despite this, the Expert Haematology Panel [59], an official UK government website for data and insights on coronavirus [60] and a group of researchers led by Pai et al. [19] stated that there is no evidence to suggest that individuals with a history of thrombosis or known risk factors for thrombosis such as pregnancy, antiphospholipid syndrome, people who use birth control or people with platelet disorders are at greater risk of VITT. This is consistent with what has been stated by Pavord et al. [10] in their retrospective and prospective cohort study about clinical features of VITT involving 220 VITT patients in the United Kingdom, in which no individual risk factors were observed. Rather, they found that VITT patients with a very low blood platelet count, CVST, intracranial bleeding, or serious coagulation activation, or patients that have all these conditions, have a higher risk of death.

As a precautionary measure, the MHRA advises individuals who develop this syndrome after the first dose of the AstraZeneca COVID-19 vaccine to not receive their second dose until the clots are fully stable [60]. When the second dose of COVID-19 vaccination can be taken, an alternative to the AstraZeneca COVID-19 vaccine should be used [60]. Additionally, for patients who are in a prothrombotic state, such as pregnant women, Pfizer and Moderna COVID-19 vaccines are preferred because of the vast experience with them, and the accessible safety data [60].

### Diagnosis

According to the available published guidelines [12-14], with the exception of the Brighton Collaboration (BC) guidelines [61], the presence of thrombosis, thrombocytopenia, and markedly high D-dimer values in the timeframe of 4 to 42 days following COVID-19 vaccination, alongside positive anti-PF4 antibodies as tested by ELISA, strongly indicates VITT/thrombocytopenia syndrome and is perfectly adequate to confirm the diagnosis, particularly in the absence of functional testing. Functional testing may be executed to supply additional data and is valuable in diagnosing complex cases of VITT. BC guidelines split the suspected VITT patients into five levels, with definite cases (level 1) meeting all the following criterion [61]: (1) new onset of thrombocytopenia, with a platelet count of less than $150\times10^9$/L, (2) no known exposure to heparin within 100 days, and (3) occurrence of thrombosis in the veins or the arteries. In the cases that have been identified, information on anti-PF4 antibodies is collected. The aspects of this guideline that differ from others include that it does not require the data on D-dimer level as the primary triaging in diagnosing VITT patients, and it does not state the usual timeframe before the onset of symptoms.

### Laboratory feature

The defining laboratory features of VITT are usually positive anti-PF4 antibody ELISA results, coupled with coagulation abnormalities such as thrombocytopenia, strikingly high level of D-dimer, and low levels of fibrinogen. A complete blood count can be conducted to ascertain the platelet count, and according to the published guideline [13,14,61,62], it has been determined that thrombocytopenia is defined as a platelet blood count less than $150\times10^9$/L. All the patients presented in the retrieved studies, excluding those with missing data, had a low blood platelet count, with the lowest one at $8\times10^9$/L [8], except two patients presented in the study by Pavord et al. [10] that had a normal blood platelet count upon admission. Pavord et al. [10] categorized their patients according to the guideline by the Expert Haematology Panel [14], which classified suspected VITT patients into four categories: definite VITT, probable VITT, possible VITT, and unlikely VITT. Since these two patients did not meet all the criteria for definite VITT, they were classified as probable VITT patients.

Another main marker that is important in the initial triaging of VITT cases is the D-dimer level [13,14,61,62]. Suspected patients of VITT have a markedly elevated level of D-dimer which is 4 times beyond the normal upper limit [13,62]. All patients for whom D-dimer level information is available have significantly elevated levels, with the highest one at 142 mg/L [8]. VITT patients presented in the studies by Sánchez van Kammen et al. [43] and Mehta et al. [33] did not have data on the D-dimer levels; the former authors followed BC

guidelines, and the latter used cases that presented early during the COVID-19 vaccination program. According to Favaloro et al. [63], if the patients have thrombocytopenia but a normal or only modestly raised D-dimer level at the time of presentation, it is more likely that they have immune thrombocytopenia (ITP) than VITT.

For screening of anti-PF4 antibodies, an ELISA is the most reliable tool [6-8], because it provides superior sensitivity and specificity for VITT testing [64]. The result of ELISA is expressed in the form of optical density, which is proportional to the concentration of antibodies present in the sample. An optical density reading >0.499 [7,38] indicates the presence of anti-PF4 antibodies. An additional functional assay such as a SRA may be performed to confirm the positive result of the ELISA test, and is needed in complex cases in which the ELISA result is negative or equivocal in the suspected VITT patient [13,15,65]. A positive anti-PF4 antibody ELISA or functional assay are the key distinguishing features of VITT from the other syndrome of thrombocytopenia and/or thrombosis such as ITP and thrombotic thrombocytopenia purpura [65].

However, not all patients in the retrieved studies had a positive ELISA result. For instance, a patient in the case report by Guetl et al. [30] reported negative anti-PF4 antibodies, but since there was a strong clinical suspicion of VITT as she fulfilled the other criteria, including the occurrence of thrombosis, thrombocytopenia, and a significantly elevated D-dimer level at an appropriate timeframe post-vaccination, the author assumed that she had VITT and was treated accordingly. Panels of the National Institute for Health and Care Excellence guidelines said that although ELISA was generally believed to be accurate and reliable, false-negative results were still possible [66]. Additionally, as stated by Platton et al. [67], despite a negative test result for PF4, VITT may still be considered since the underlying pathology for CVST depends on the patient's history. Therefore, a person who satisfies all the criteria for VITT but whose ELISA result is negative may still be suspected of having the syndrome. Besides, not all patients in the retrieved studies underwent an ELISA test. One of the reasons behind this could be because ELISA assays are not widely available in diagnostic laboratories [67].

To summarize, all the patients present in the retrieved studies satisfied these three laboratory findings with the exception of those that lacked data, those with no samples available, those for whom this test was not performed because of death or because a different guideline was followed by the authors, or the few cases that were initially presented during the early stages of the COVID-19 vaccination program.

### Imaging findings

For people for whom there is a high clinical suspicion of VITT, imaging tests should be performed on the same day based on the location of symptoms before initiation of any therapy to verify thromboembolism. Unenhanced CT of the brain is a rational primary diagnostic imaging test for individuals with suspected CVST because it can eliminate other differential diagnoses, including ICH that has nonspecific and similar neurologic symptoms such as headaches [68]. However, the sensitivity of unenhanced CT is insufficient to exclude CVST [68]. Therefore, it is imperative that both vascular and parenchymal imaging are carried out simultaneously, either with an urgent non-contrast CT head and a CTA/CT venogram (CTV), or with an urgent MRI head and a contrast-enhanced MRV [16,68]. From the retrieved studies, in diagnosing and confirming CVST, the following imaging tools were used: CT scan (14 studies) [6,10,22-28,34-36,38,39], MRI (seven studies) [10,27,34,36,38,43,45], MRV (three studies) [34,38,43], CTV (seven studies) [6,22,23,29,39,42,43], and CTA (five studies) [27,28,32,37,38].

To diagnose SVT, Doppler ultrasound and CT with contrast are commonly employed [16,69]. If the patient is highly suspected of having portal vein thrombosis, it is best to start with an abdominal CT scan or MRI instead of an ultrasound [69]. A CT scan is advantageous because it reveals any additional pathology that may be present, such as a cancerous tumor [69]. In cases where splenic vein thrombosis is suspected, Doppler ultrasound is the diagnostic test of choice. A diagnosis of splenic vein thrombosis is pretty unlikely if the splenic vein Doppler ultrasound is normal [69]. Doppler ultrasound is also the most suitable for diagnosing hepatic venous thrombosis, and after the diagnosis has been made, a CT scan of the abdomen or an MRI may be performed to confirm this [69]. To diagnose mesenteric vein thrombosis, a CT scan of the abdomen is the first line diagnostic tool since it has a 90% accuracy rate [69]. However, in cases where a CT scan is non-diagnostic, CTA is recommended to be performed [69]. Mesenteric venous thrombosis, on the other hand, is best visualized using MRV, but it is not necessary in the majority of cases because CT scans are sufficient [69]. From the retrieved studies, in diagnosing and confirming SVT, the following imaging tools were used: CT abdominal and pelvis (six studies) [6,8,9,22,34,41], abdominal CTA (two studies) [34,40], abdominal ultrasound (two studies) [35,38], and Duplex ultrasound (one study) [40].

Compression ultrasonography with Doppler is the imaging

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modality that is frequently used for identification of DVT [16]. This imaging tool is non-invasive with superior performance that is simple, safe, practical, extremely sensitive, and specific for the detection of lower extremity DVTs without requiring the use of radiation or contrast exposure [70-72]. From the gathered studies, two studies [36,37] used Doppler ultrasound and another two studies [31,38] utilized lower extremity ultrasound in diagnosing and confirming DVT.

CTPA is the gold standard for diagnosing PE [73] because it is very sensitive (83%), specific (96%) [74], widely accessible, minimally invasive, rapid, has the ability to directly visualize emboli in the pulmonary vasculature, and can provide alternative diagnoses [75]. The prognosis of acute PE is primarily determined by the residual pulmonary circulation and the degree of right ventricular (RV) dysfunction [76]. Since CTPA possess additional prognostic value in which it can assess RV function, it can predict the severity of PE as well as the patient's prognosis [75]. From the gathered studies, four studies use CTPA in diagnosing and confirming the presence of PE [23,30,32,41]. Meanwhile another two studies employed chest CTA instead of CTPA [37,38].

The brain and its arteries can be visualized in great detail using MRI and MRA; hence, these can be used for detecting an ischemic stroke [77]. Even though CT is as effective as MRI at locating blood, an MRI is remarkably accurate in diagnosing an acute ischemic stroke and its cause [77] since it is more sensitive and provides a more comprehensive picture [78]. A case report by Blauenfeldt et al. [9] and Malik et al. [32] mentioned the use of MRI and head CT in respectively diagnosing and confirming an ischemic stroke.

All the VITT patients from the presented studies had thrombosis except one patient in a case series by Scully et al. [7] that only experienced hemorrhagic symptoms. This patient however had a positive anti-PF4 antibody ELISA test, thrombocytopenia as well as D-dimer elevation. In this case, Pavord et al. [10] stated that that the lack of thrombosis was most likely due to the early detection and treatment of VITT.

### Management

According to the published guidelines, for managing the immune responses in VITT, it is recommended to immediately treat patients with IVIG at 0.5 to 1 g per kg daily for 2 days, especially if the patient has a blood platelet count of less than $50\times10^9$/L [13,14,62,66]. If there is insufficient response to treatment after 2 to 3 days, as evidenced by no improvement in blood platelet count or development or progression of thrombosis, it is reasonable to consider a second dose of IVIG or adding another type of treatment including steroids (methylprednisolone, dexamethasone, or prednisolone), plasma exchange, or monoclonal antibody (rituximab or eculizumab) [10,62,66]. Plasma exchange [13,14,62,66,79] can be considered to reduce the high antibody burden in patients with poor prognosis such as having severe thrombocytopenia (blood platelet count less than $30\times10^9$/L), secondary bleeding, a fibrinogen level less than 1 g/L, CVST, multiple organ thrombosis [13,66], or progressed thrombosis [62] despite being given IVIG, steroid, and non-heparin anticoagulant treatments [13,62]. From the retrieved studies, 18 studies utilized IVIG as the initial treatment for managing the immune responses [6,10,23,26,29-39,42-44], and 16 studies reported the use of another class of drug, which is steroids, as the second line treatment for these immune-mediated disorders [6,9,10,23,26,30,31,33,36-39,41-44]. Besides, five studies employed plasma exchange as a salvage therapy for patients [10,37,41-43]. Sangli et al. [37] described the use of plasma exchange when DVT had progressed and a new upper DVT develops even after the administration of IVIG and steroids. Pavord et al. [10]. reported the utilization of plasma exchange in 17 patients who suffered with disease involving CVST, multiple thrombosis or both. Monoclonal antibodies such as eculizumab and rituximab have also been administered as second line immunomodulation treatment of VITT in two cases [43,44]. In a case report by Tiede et al. [44], eculizumab was used in two patients, one because of thrombotic microangiopathy and renal failure, while in another patient, the drug acted as rescue therapy because of a severe thromboembolic event despite the use of IVIG and while on anticoagulation. The rationale behind the use of monoclonal antibody is because, in addition to the Fc receptor–dependent platelet activation that is addressed by IVIG, PF4 and anti-PF4 immune complexes can also trigger the complement system via the classical pathway, which is triggered by the antigen–antibody interactions [79]. Therefore, monoclonal antibody is another suitable choice in dampening the immune-complex-driven thrombus inflammation, by preventing the activation of the complement protein.

For managing thrombosis, if the platelet count of the patient is greater than $50\times10^9$/L and there is no evidence of significant bleeding [13], a non-heparin anticoagulant such as direct oral anticoagulant (apixaban or rivaroxaban) or parenteral direct thrombin inhibitors (bivalirudin or argatroban) can be administered [13,62,66]. The selection among these agents will depend on the drug profile and is specific to the patient's condition [79]. Parenteral direct thrombin inhibitors are strongly recommended for critically ill VITT patients with very low blood platelet count–less than $30\times10^9$/L–due to their intravenous route of administration and

short half-life [66]. Twenty-four of the 26 retrieved studies employed various types of anticoagulation in treating the thrombosis, with non-heparin anticoagulant being the most prevalent [6,8-10,23,25,26,29-45]. Some studies that initially used heparin or low molecular weight heparin (LMWH) switched to non-heparin anticoagulation after a positive PF4 result was confirmed or after VITT cases were suspected [8,23,34,37,38,40]. A majority of the published guidelines recommend the use of a non-heparin anticoagulant because of its proven safety and effectiveness [13,14,62,66]. Heparin or LMWH must be avoided in the treatment of VITT due to the lack of consensus regarding their safety [62].

Prophylactic platelet transfusions might aggravate the development of VITT because human platelets store PF4, the antigenic target of the antibodies in VITT [79]. Therefore, such transfusions must be avoided in treating suspected or diagnosed VITT patients [13,62,66,80] unless there is a presence of massive bleeding [79] or a need for surgical intervention (that usually results from the sequelae of CVST) in removing the thrombosis [13,62,66]. In this case, platelet transfusion or fibrinogen replacement are needed to be executed before the surgery in order to reduce the risk of bleeding [66] and to augment intraoperative coagulation [81]. However, platelet transfusions should only be accomplished after IVIG administration [81]. From the findings, 13 studies utilized platelet transfusion and fibrinogen replacement in treating VITT patients [6,8,9,23,25,28,33,36-38,40,42,43].

Neurosurgical intervention, including decompressive craniectomy, is also required, particularly when there is elevated pressure in the brain as a result of ICH secondary to CVST [81]. The preoperative anticoagulant of choice for patients that have bleeding due to thrombosis or anticoagulation is argatroban [81]. Due to its short half-life, it can be stopped with an adequate preoperative measure without the need for a reversal agent [82]. Furthermore, for postoperative anticoagulation in these patients, Kuramatsu et al. [83] recommend initiating therapeutic anticoagulation on day 6, but only for those who are at high risk of a thromboembolic event. As seen from the findings, neurosurgery was performed on VITT patients in 11 studies [6,9,10,23,25,28,36,39,42,43,45], particularly those who had CVST.

## Conclusion

VITT cases are strongly related to viral vector-based vaccines, particularly the AstraZeneca COVID-19 vaccine, with much rarer reports involving mRNA-based vaccines such as the Moderna COVID-19 vaccine and the Pfizer COVID-19 vaccine. CVST is the most dominant manifestation of this syndrome with headache as the first primary symptom. In term of its management, IVIG and non-heparin anticoagulant are the main therapeutic options for managing immune responses and thrombosis, respectively. It is hoped that future research could explore the high incidence of CVST in VITT patients and determine the possible causes before a definite conclusion can be drawn.

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