Vaccine-induced thrombotic thrombocytopenia following coronavirus vaccine: A narrative review

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\textbf{ABSTRACT}

The novel coronavirus pandemic has taken a toll on the global healthcare systems and economy. Safety precautions, along with vaccination, are the most effective preventive measures. The global vaccination program against COVID-19 has dramatically reduced the number of deaths and cases. However, the incidence of thrombotic events and thrombocytopenia post-COVID-19 vaccination known as vaccine-induced thrombotic thrombocytopenia has raised safety concerns. This has led to an element of vaccine hesitancy. The exact mechanism for vaccine-induced thrombotic thrombocytopenia is unknown. Although the incidence of thrombosis associated with COVID-19 vaccination is low, it still requires attention, especially in older people, smokers, and people with preexisting comorbidities. This study aims to review the pathophysiology, diagnosis, and management of vaccine-induced thrombotic thrombocytopenia, to provide a concise and comprehensive update.

\section{Introduction}

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) cases were initially reported in Wuhan, China, towards the end of 2019. Following its extensive spread, the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020 \cite{1}. To the date, April 16, approximately 207 million confirmed cases have been reported, and 4.3 million deaths \cite{2}.

Coordinated global efforts led to the development of COVID-19 vaccines, followed by emergency use authorization within nine months of the pandemic \cite{3}. These vaccines are now widely available for public administration \cite{4}. The vaccines are safe and effective in preventing severe infection, hospitalization, and death \cite{5,6}. To date, 4.4 billion vaccine doses have been administered \cite{2}. The common adverse effects following COVID-19 vaccination are injection site pain and transient, self-limited systemic symptoms like headache, fever, myalgias, etc. \cite{7}.

Recently, a more severe adverse effect, thrombocytopenia with or without thrombosis, has been reported following SARS-CoV-2 vaccination. Thrombocytopenia is a medical condition characterized by platelets lower than 150,000/microliter and is associated with a risk of bleeding and thrombosis \cite{8}. Such reports have raised concerns over the safety profile and hesitancy towards the available vaccines \cite{9}. The term “Vaccine-Induced Thrombotic Thrombocytopenia” describes post-vaccination thrombocytopenia cases. VITT is characterized by thrombosis at unusual sites and thrombocytopenia following vaccination \cite{9}.

While VITT has been associated with both mRNA and viral vector vaccines, its prevalence is higher in viral vectored vaccines \cite{7}. Following the incidence of 30 thromboembolism cases in March 2021, Oxford/AstraZeneca (AZD1222) was transiently suspended in numerous European countries \cite{10}. Later the pharmacovigilance risk assessment committee (PRAC) of the European medical agency (EMA) reviewed all cases and declared thrombosis and thrombocytopenia as rare adverse effects of AZD1222. However, based on risk-benefit assessment, the vaccine was later declared safe for use \cite{11}. Owing to a similar reason, in April 2021, Johnson & Johnson’s Janssen (Ad26.Cov2-S) administration was also temporarily suspended \cite{12}.

Herein, we review the association between SARS-CoV-2 vaccines and VITT. This review evaluates the potential pathophysiology and clinical
approach to diagnoses and management of VITT.

1.1. Literature review

The work has been reported in line with the PRISMA 2020 criteria [13]. Two authors (SHA, SW) dependently conducted a thorough literature search over PubMed and Clinicaltrials.gov from inception till August 16, 2021, without any language restriction. To achieve comprehensive results, search string comprised of keywords, “SARS-CoV-2 Vaccine”, “Coronavirus Vaccine,” “Corona Vaccine,” “COVID-19 Vaccine”, “thrombotic thrombocytopenic,” “Vaccine-Induced Thrombotic Thrombocytopenia,” “VITT,” “thrombocytopenia,” “reduced platelet count,” using BOOLEAN operators. Synonyms, related terms, and spelling variants were also engaged. All relevant case reports, case series, cohort studies, editorials, and correspondences were reviewed. Any discrepancies were resolved via discussion with a third reviewer (IU). The results of the literature search are shown in Fig. 1. Following studies selection, two independent authors (TGS, NAQ) extracted all the relevant data into a table comprising of author’s name, patient’s age, and sex, past medical history, presenting complaint, laboratory findings, radiological findings, treatment interventions, and outcome. Any discrepancies were resolved by discussion with a third reviewer (IU). All significant findings are summarized in Table 1.

1.2. Demographics

The retrieved studies comprise data of 44 patients (32 females, 11 males, 1 not defined) with a mean age of 44.9 ± 14.3 years. The following figure (Fig. 2) depicts the geographical distribution of the reported cases around the globe, with the majority of cases arising in Europe. Based on these and future reporting, we can predict the potential spatial spread, geographical locations that may be more susceptible than others and this may help us establish links between different genetic and environmental factors, predisposing an individual to such consequences of vaccines.

1.3. Pathophysiology

The exact pathophysiology behind VITT is unclear. As shown in Table 1, most of the cases presented with thrombocytopenia, elevated D-dimer, and positive titers of IgG antibodies against platelet factor 4 (PF-4) [14–22]. Based on these findings, this syndrome is closely related to heparin-induced thrombocytopenia (HIT), a medical condition characterized by thrombocytopenia, and the presence of antibodies against the Heparin-PF4 complex [23].

HIT, an autoimmune reaction to heparin, involves the generation of IgG antibodies against the Heparin-PF4 complex. The Fc portion of these antibodies adheres to the complex, binds to the FcYRIIa receptors [24], and initiates platelets activation via intracellular signaling involving spleen tyrosine kinase [25]. This results in the release of microparticles and a procoagulant state [26,27]. Furthermore, clearance of activated and antibody-bound platelets by the reticuloendothelial system culminates in thrombocytopenia [28]. A prerequisite in the diagnosis of HIT includes a known recent exposure to heparin. A condition labeled “Autoimmune Heparin-Induced Thrombocytopenia (aHIT)” manifests with clinical and laboratory findings without any prior use of heparin [29]. Based on this resemblance, a comparison has been drawn between VITT and variants of aHIT [30], and hence, we may assume that a similar mechanism follows post-vaccination. However, the mechanism behind the generation of these antibodies is yet to be elucidated.

In HIT, the electrostatic interaction between positively charged PF4 and negatively charged heparin culminates in the formation of the
| Author                  | Sex and Age | Past Medical history | Presenting Complaint | Vaccine administered | Laboratory findings | Radiological findings | Intervention | Outcome   |
|------------------------|-------------|----------------------|----------------------|----------------------|---------------------|------------------------|--------------|-----------|
| Al-Maqbali et al. [56] | 59 y/o Female | Type 2 diabetes mellitus, osteoarthritis, and COVID-19 pneumonia in September 2020, OCP | Sudden onset left leg pain 7 days after receiving her first dose. | Pfizer-BioNTech mRNA | Platelet = 182 x 10⁹/L, D-dimer = 42 mg/L | Bifurcation of the pulmonary trunk and main pulmonary arteries emboli extending to the lobar and subsegmental branches | Rivaroxaban 2 x 15 mg daily for 21 days, followed by rivaroxaban 20 mg daily for a total of 3 months | Recovered |
| Muir et al. [56]       | 48 y/o Male | | 3 days history of malaise and abdominal pain | Ad26.COV2.S vaccine (Johnson & Johnson/Janssen) | Platelet = 34 x 10⁹/L, D-dimer = 6000 ng/mL | Cerebral venous sinus thrombosis involving the right transverse and straight sinuses and extensive splenial vein thrombosis | Argatroban & IVIG at a dose of 1 g/kg of ideal body weight | Critically ill at the time of the report |
| Sheikh et al. [57]     | 50 y/o Male | | Headache, vertigo, and vision changes | ChAdOx1 nCoV-19 (AstraZeneca) | N/A | Central venous sinus thrombosis (CVST) in transverse and sigmoid sinuses | Desirudin, IVIG at 1 g/kg/hour and Prednisolone at 1 mg/kg daily | Recovered |
| Ramadan et al. [58]    | 54 y/o Male | Rare congenital limb malformation | 7-day history of worsening headache, bruising and unilateral right calf swelling | ChAdOx1 nCoV-19 (AstraZeneca) | Platelet = 24 x 10⁹/L, D-dimer = 5620 ng/mL | Extensive cerebral venous sinus thrombosis | Therapeutic IVIG and anticoagulation | Recovered |
| Bano et al. [49]       | 53 y/o Female | | Worsening headache and weakness of the right arm and leg | ChAdOx1 nCoV-19 (AstraZeneca) | Platelet = 25 x 10⁹/L, D-dimer = 9976 ng/mL | Cerebral Venous sinus thrombosis | Three units of platelets were transfused before urgent neurosurgical intervention | Death |
| Bano et al. [49]       | 61 y/o Female | | 3-day history of progressive dyspnea, pain, and swelling in the right leg | ChAdOx1 nCoV-19 (AstraZeneca) | Platelet = 119 x 10⁹/L | Small cerebellar hemorrhage, CSVT in the inferior sagittal sinus, vein of Galen and straight, right transverse and sigmoid sinuses. Bilateral segmental pulmonary embolism, thrombosis in uterine veins. | IV, steroids, warfarin | Recovered |
| Wiedmann et al. [59]   | 42 y/o Female | | Severe headaches, nausea, vomiting, fluctuating level of consciousness, and right-sided hemiparesis | ChAdOx1 nCoV-19 (AstraZeneca) | N/A | Left transverse sinus and sigmoid sinus vein thrombosis (CSVT) and cortical vein thrombosis | IV methylprednisolone (1 mg/kg) daily and IVIG (1 g/kg) for 2 days | Death |
| Wiedmann et al. [59]   | 37 y/o Female | | 2-day history of headaches, fever, transient numbness in the right foot, and right-sided visual disturbance | ChAdOx1 nCoV-19 (AstraZeneca) | N/A | CSVT in the left transverse and sigmoid sinus and left occipital CSVT | Urgent suboccipital craniectomy was performed and cerebellar herniation encountered during surgery | Death |
| Wiedmann et al. [59]   | 39 y/o Female | | Abdominal pain and headaches | ChAdOx1 nCoV-19 (AstraZeneca) | Platelet = 2 x 10⁹/L | Small cerebellar hemorrhage, CSVT in the inferior sagittal sinus, vein of Galen and straight, right transverse and sigmoid sinuses. Bilateral segmental pulmonary embolism, thrombosis in uterine veins. | IV, steroids, warfarin | Recovered |
| Wiedmann et al. [59]   | 54 y/o Female | | | ChAdOx1 nCoV-19 (AstraZeneca) | N/A | CSVT in nearly all major venous sinuses | Methylprednisolone (1 mg/kg) and IVIG (1 g/kg) for 2 days and decompressive hemi-craniecotomy | Death |
| Ruhe et al. [51]       | 84 y/o Female | | Partial hemiplegia, scattered petechiae, | | | Corticosteroid and plasma exchange | Recovering |

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| Author                        | Sex and Age | Past Medical history | Presenting Complaint                                      | Vaccine administered | Laboratory findings | Radiological findings | Intervention                                      | Outcome   |
|------------------------------|-------------|----------------------|-----------------------------------------------------------|----------------------|---------------------|-----------------------|---------------------------------------------------|-----------|
| S.H. Ahmed et al. [50]       | Female      | N/A                  | and severe arterial hypertension.                        | Pfizer-BioNTech mRNA | Platelet count = 45 × 10^9/L | Multiple subacut emboli without vessel occlusion. | therapy (PEX) with fresh frozen plasma. Rituximab at day 2 as second corticosteroid IVlg at 1 g/kg, Argatroban and corticosteroids. Platelet therapy was administered before the decompressive surgery. During operation, artificial hemostyptics and transfusions were done. | Death     |
| Gesseler et al. [60]         | 47 y/o      | Female               | Progressive headache 7 days after the first dose         | ChAdOx1 nCoV-19 (AstraZeneca) | Platelet = 9 × 10^9/L, D-dimer >35.2 mg/L | Large-scale sinus thrombosis | IVlg at 1 g/kg, Argatroban and corticosteroids. Platelet therapy was administered before the decompressive surgery. During operation, artificial hemostyptics and transfusions were done. | Death     |
| Gesseler et al. [60]         | 50 y/o      | Female               | Progressive headache 10 days after first dose            | ChAdOx1 nCoV-19 (AstraZeneca) | Platelet = 24 × 10^9/L, D-dimer >35.2 mg/L | Large-scale sinus thrombosis | IVlg at 1 g/kg, Argatroban and corticosteroids. Platelet therapy was administered before the decompressive surgery. During operation, artificial hemostyptics and transfusions were done. | Death     |
| Gesseler et al. [60]         | 44 y/o      | Female               | Progressive headache 12 days after the first dose         | Ad26.COV2. S vaccine (Johnson & Johnson/ Janssen) | Platelet = 48 × 10^9/L, D-dimer >35.2 mg/L | Large-scale sinus thrombosis | IVlg at 1 g/kg, Argatroban and corticosteroids. Platelet therapy was administered before the decompressive surgery. During operation, artificial hemostyptics and transfusions were done. | Death     |
| Patel et al. [15]            | 33 y/o      | Male                 | Back pain, hematuria, headache, and right leg pain for 1 week | ChAdOx1 nCoV-19 (AstraZeneca) | D-dimer >20 mg/L, Anti-PF4 antibodies were positive | Elevated D-dimers and positive anti-PF4 antibodies | IV Argatroban, IVIG, and warfarin | Recovered |
| Patel et al. [15]            | 28 y/o      | Male                 | Back pain and lower limb weakness                         | ChAdOx1 nCoV-19 (AstraZeneca) | Platelets = 12 × 10^9/L, Anti-P4 antibodies were positive | Cerebral venous sinus thrombosis. | IVlg (1 g/kg) once a day, Dabigatran, Idarucizumab, Prednisolone once daily (1 mg/kg) with proton pump inhibitors cover | Death     |
| Patel et al. [15]            | 61 y/o      | Male                 | Exertional dyspnea and pleuritic chest pain               | ChAdOx1 nCoV-19 (AstraZeneca) | Platelets = 30 × 10^9/L | Superior sagittal sinus and cortical vein thrombosis | No treatment since the condition continued to deteriorate | Death     |
| Suresh et al. [17]           | 27 y/o      | Male                 | Intermittent headaches associated with eye floaters       | ChAdOx1 nCoV-19 (AstraZeneca) | Platelets = 19 × 10^9/L, Positive anti-P4 antibodies | Superior sagittal sinus thrombosis with cortical veins involvement. | Intravenous unfractionated heparin, platelet transfusions, IV dexamethasone, IVIG, and intravenous le✈ develacetam | Death     |
| Mehta et al. [16]            | 32 y/o      | Male                 | Thunderclap headache, subsequent left-sided incoordination, and hemiparesis | ChAdOx1 vaccine (AZD1222, Vaxzevria) | Platelets = 73 × 10^9/L, D-dimer = 17548 μ/L | Pulmonary emboli, right ventricle thrombus, and splenic vein thrombus | Apixaban, infusion, ventilation, plasma exchange, IV methylprednisolone, and heparin infusion | Recovered |
| Mehta et al. [16]            | 25 y/o      | Male                 | Primary sclerosing cholangitis and migraines             | ChAdOx1 vaccine (AZD1222, Vaxzevria) | Platelets = 51 × 10^9/L | Superior sagittal sinus thrombosis with cortical veins involvement. | Intravenous unfractionated heparin, platelet transfusions, IV dexamethasone, IVIG, and intravenous le✈ develacetam | Death     |
| Xie et al. [50]              | 23 y/o      | N/A                  | Chest pain and breathlessness                            | N/A                  | Platelets = 73 × 10^9/L, D-dimer = 17548 μ/L | Pulmonary emboli, right ventricle thrombus, and splenic vein thrombus | Apixaban, infusion, ventilation, plasma exchange, IV methylprednisolone, and heparin infusion | Recovered |
| Sorensen et al. [22]         | 33 y/o      | Female               | Headache and general malaise                             | N/A                  | Platelets = 10 × 10^9/L | Tinzaparin, Fondaparinux | | Recovered |

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Table 1 (continued)

| Author          | Sex and Age | Past Medical history                                                                 | Presenting Complaint                                                                 | Vaccine administered                  | Laboratory findings                                      | Radiological findings                               | Intervention                                           | Outcome       |
|-----------------|-------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------|----------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|---------------|
| Dias et al.     | 47 y/o Female | Iron deficiency anemia due to adenomyosis                                             | Headache, nausea, and photophobia                                                    | Pfizer-BioNTech mRNA                 | Platelets = 34000/mL Positive Anti-PF4 antibodies          | Cerebral venous sinus thrombosis and portal vein thrombosis | Acetazolamide, enoxaparin 60 mg, and warfarin           | Recovered     |
|                 |             |                                                                                      |                                                                                      |                                       | D-dimer > 62/nl Anti-PF4 antibodies Negative                              | Thrombosis of superior sagittal, right lateral, transverse, sigmoid sinuses and jugular vein and left sigmoid sinus | Levotiracetam 500 mg, enoxaparin 80 mg, dabigatran 150 mg | Recovered     |
| Dias et al.     | 67 y/o Female | Multiple cerebral cavernous malformations, hypertension, diabetes, dyslipidemia, viral myocarditis, and depression | Right lower limb clonic movements, motor deficit, loss of consciousness, and headache | Pfizer-BioNTech mRNA                 | Platelets = 164000/mL Positive Anti-PF4 antibodies          | Thrombosis of high convexity cortical veins, superior sagittal, right transverse, and sigmoid sinus and jugular vein | Levetiracetam 500 mg, enoxaparin 80 mg, dabigatran 150 mg | Recovered     |
| Tiede et al.    | 63 y/o Female | N/A                                                                                  | Headache, somnolence, dysphasia, right-sided hemiparesis, and arterial hypertension    | ChAdOx1 nCoV-19 (AZD1222, Vaxzevria) | Platelets = 27/µL D-dimer > 35.2 mg/L Anti-PF4 antibodies Positive | Left transverse and sigmoid sinus thrombosis, cerebral venous sinus thrombosis | Heparin and eculizumab                                   | Recovering    |
| Tiede et al.    | 67 y/o Female | N/A                                                                                  | Headache                                                                            | ChAdOx1 vaccine (AZD1222, Vaxzevria) | Platelets = 40/µL D-dimer > 35.2 mg/L Anti-PF4 antibodies Positive | Aortic arch thrombi and cerebral arterial embolism       | Argatroban and IVIG                                      | Recovered     |
| Tiede et al.    | 61 y/o Female | N/A                                                                                  | Fatigue                                                                             | ChAdOx1 vaccine (AZD1222, Vaxzevria) | Platelets = 12/µL D-dimer > 35.2 mg/L Anti-PF4 antibodies Positive | Splanchnic vein thrombosis                             | Argatroban, IVIG, alteplase, eculizumab                 | Recovering    |
| Tiede et al.    | 61 y/o Female | N/A                                                                                  | Headache, dysarthria, left-sided hemiplegia, conjugated gaze palsy                    | ChAdOx1 vaccine (AZD1222, Vaxzevria) | Platelets = 62/µL D-dimer > 35.2 mg/L Anti-PF4 antibodies Positive | Right internal carotid and middle cerebral artery (M1) thrombosis and cerebral arterial thrombosis | Argatroban and IVIG                                      | Recovering    |
| Guejl et al.    | 50 y/o Female | N/A                                                                                  | Severe headache and severe back pain                                                 | ChAdOx1 nCoV-19 (AstraZeneca)        | Platelets = 27 × 10³/µL D-dimer > 33 mg/L Anti-PF4 antibodies Positive | Multifocal thrombus in the pelvic region and embolus in the posterior–basal right lower lobe | IVIG, dexamethasone 40 mg, argatroban, and dabigatran | Recovered     |
| Schultz et al.  | 37 y/o Female | Pollen allergy                                                                       | Headaches, fever, and visual disturbance                                              | ChAdOx1 nCoV-19 (AstraZeneca)        | Platelets = 22000 mm³ D-dimer > 35 mg/L Anti-PF4 antibodies Negative | Thrombosis in the left transverse, left sigmoid sinuses, and cortical veins | Dalteparin, platelet, and decompressive craniotomy      | Death         |
| Schultz et al.  | 42 y/o Female | Pollen allergy                                                                       | Headache and drowsiness                                                               | ChAdOx1 nCoV-19 (AstraZeneca)        | Platelets = 14000 mm³ D-dimer > 35 mg/L Anti-PF4 antibodies Negative | Thrombosis in the left transverse left sigmoid sinuses and cortical veins | Dalteparin, platelet transfusion, IVIg 1 g/kg, methylprednisolone 1 mg/kg, and hemicrianiectomy | Death         |
| Schultz et al.  | 32 y/o Male  | Asthma                                                                               | Back pain                                                                            | ChAdOx1 nCoV-19 (AstraZeneca)        | Platelets = 10,000 mm³ D-dimer > 35 mg/L Anti-PF4 antibodies Negative | Thrombosis of portal vein branches                      | Dalteparin, prednisolone 1 mg/kg, and hemicrianiectomy | Recovered     |
| Schultz et al.  | 39 y/o Female | N/A                                                                                  | Headache and abdominal pain                                                           | ChAdOx1 nCoV-19 (AstraZeneca)        | Platelets = 70000 mm³ D-dimer > 35 mg/L Anti-PF4 antibodies Negative | Thrombosis of Inferior sagittal sinus, straight sinus, the vein of Galen, right | IVIg 1 g/kg, prednisolone 1 mg/kg, dalteparin, warfarin | Recovered     |

(continued on next page)
Table 1 (continued)

| Author            | Sex and Age | Past Medical history                                                                 | Presenting Complaint                                      | Vaccine administered                  | Laboratory findings                     | Radiological findings                                           | Intervention                                                                 | Outcome     |
|-------------------|-------------|--------------------------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------|-----------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------|-------------|
| Schultz et al.    | 54 y/o      | Female                                                                               | Hypertension and hemiparesis                             | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 19000 mm$^3$               | transverse sinus, and right sigmoid sinus                         | IVIg 1 g/kg, methylprednisolone 1 mg/kg                              | Death        |
| Malik et al.      | 43 y/o      | Female                                                                               | Hyperlipidemia, anxiety, depression, obesity, obstructive sleep apnea, and gastroesophageal disease | Ad26.COV2. S vaccine (Johnson & Johnson/Janssen) | Platelets = 27 × 10$^3$/L D-dimer = 35.2 mg/L Anti-PF4 antibodies were positive | Pulmonary embolism and intracerebral thrombus                      | IVIg, fondaparinux, floriect and topirimate                         | Recovered    |
| Garnier et al.    | 26 y/o      | Female                                                                               | N/A                                                      | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 80 × 10$^3$/L Anti-PF4 antibodies were positive | Occlusion in middle cerebral artery                                | Corticosteroids, anticoagulants, and plasma exchange                 | N/A          |
| Abadi et al.      | 30 y/o      | Female                                                                               | Headache, neck pain, lower extremity pain, and weakness | Ad26.COV2. S vaccine (Johnson & Johnson/Janssen) | Platelets = 32000/μL D-dimer = 10 mg/mL Anti-PF4 antibodies were positive | Acute deep vein thrombosis involving posterior tibials and popliteal veins, obstructive thrombosis in right transverse sinus extending to right sigmoid sinus and jugular bulb, pulmonary embolism | Argatroban and bivalirudin                                          | Recovered    |
| Agostino et al.   | 54 y/o      | Female                                                                               | Acute cerebrovascular accident                           | ChAdOx1 nCoV-19 (AstraZeneca)         | Normal D-dimer                         | Deep vein thrombosis, acute basilar thrombosis                   | Initially low molecular weight heparin, anti-hypertensive, oral double (dabigatran 110 mg/die = rivaroxaban 30 mg/die) anticoagulants, IV methylprednisolone, dabigatran antagonist, and a decompressive cranietomy | Death       |
| Mauriello et al.  | 48 y/o      | Female                                                                               | Penicillin allergy, episode of thrombocytopenia in 2016, Postmortem analysis indicated pre-existing thrombocytopenia | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 2590 ng/mL Anti-PF4 antibodies were positive | Thrombo-embolic filling defects affecting the pulmonary artery, sigmoid transverse sinus thrombosis, right internal jugular vein thrombosis, right temporo-occipital intraparenchymal hemorrhage | Endovascular rheolysis, 2 × 1000 mg levetiracetam (PO) daily for three months, 2 × 80 mg enoxaparin sodium (SC) daily for ten days, followed by direct oral anticoagulation with 2 × 150 mg dabigatran PO daily for six months | Recovered    |
| Wolf et al.       | 22 y/o      | Female                                                                               | Shivering, fever, and headaches for two days, with spontaneous resolution Day 4: New frontally accentuated headaches Day 7: A self-limited generalized epileptic seizure occurred. | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 75000/μL D-dimer = 2590 ng/mL Anti-PF4 antibodies were positive | Superior sagittal sinus, left side transverse sinus, sigmoid sinus, and ascending cerebral veins thrombosis. | Endovascular rheolysis in two separate sessions, 2 × 80 mg SC Enoxaparin for 2 days then changed to 3 × 750 mg Danaparoid 2250 IU danaparoid SC, endovascular rheolysis, 2 × 60 mg enoxaparin sodium SC daily for one week, followed by direct oral anticoagulation with 2 × 150 mg dabigatran PO daily for six months | Recovered    |
| Wolf et al.       | 46 y/o      | Female                                                                               | Severe headaches eight days after the first dose          | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 60,000/μl Anti-PF4 antibodies were positive | Superior sagittal sinus, left-hand transverse sinus, sigmoid sinus thrombosis. | Endovascular rheolysis                                           | Recovered    |
| Wolf et al.       | 36 y/o      | Female                                                                               | Severe headaches seven days after the first dose, three days of fever and headache, acute somnolence, and right-hand hemiparesis | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 92000/μl Anti-PF4 antibodies were positive | Straight sinus thrombosis, non-occlusive thrombus in the superior sagittal sinus | Endovascular rheolysis in two separate sessions, 2 × 80 mg SC Enoxaparin for 2 days then changed to 3 × 750 mg Danaparoid 2250 IU danaparoid SC, endovascular rheolysis, 2 × 60 mg enoxaparin sodium SC daily for one week, followed by direct oral anticoagulation with 2 × 150 mg dabigatran PO daily for six months | Recovered    |
| Bjørnstad-Tuveng et al. | Female in her 30s | An uncomplicated birth 11 months prior with 1500 mL bleeding, mild | Headache after 7 days of vaccination. This was followed by a worsening | ChAdOx1 nCoV-19 (AstraZeneca)         | Platelets = 37 × 10$^3$/L D-dimer > 7.0 mg/L | Postmortem examination revealed fresh small thrombi in the transverse sinus, 1 g of tranexamic acid intravenously, midazolam for seizure | Death |
Heparin-PF4 complex [31]. This phenomenon has also been observed with other negatively charged molecules like numerous polyphosphates [32], Polyvinyl phosphonate [33], nucleic acids [34], etc. According to Visentin et al. [33], numerous negatively charged molecules, spaced about 0.5 nm apart along the molecular backbone and of sufficient length, can form complexes with PF4 while being detectable by the antibodies. Hence, components of vaccines can be expected to play a crucial role in the generation of PF4-polyanions complex and antibodies against them. Moreover, environmental factors and genetic predisposition can exacerbate clinical presentation. For example, specific genotypes encoding FcRIIA have been associated with an increased risk of thrombosis in individuals with anti-PF4-polyanion antibodies [24].

Another postulated mechanism involves cross-reactivity of anti-SARS-CoV-2 spike protein antibodies that generates following SARS-CoV-2 vaccination with PF4. This may be attributable to molecular mimicry, a phenomenon whereby a certain degree of resemblance exists between the pathogens and the host’s antigens [35]. Kanduc et al. [36] report massive homogeneity between the SARS-CoV-2 spike glycoprotein and human proteins, thus further strengthening this hypothesis. This structural resemblance can also explain the findings of thrombocytopenia [37] and anti-PF4 antibodies [38] in certain SARS-CoV-2 patients. However, the currently available literature suggests no evidence of cross-reactivity [38,39].

Zhang et al. [40] investigated the findings of thrombosis and thrombocytopenia in SARS-CoV-2 patients. They reported spike protein’s ability to stimulate platelet activation and thrombus formation via the Mitogen-activated protein kinase (MAPK) pathway. Based on the findings [40], the generation of spike protein following vaccination can also play a pivotal role in inducing thrombocytopenia and thrombosis via spike protein-ACE2 interaction-induced platelets activation. However, it remains unanswered if similar interactions can be observed post-vaccination with vector or mRNA vaccines. Moreover, some evidence [41] reveals potential interactions between adenovirus particles and circulating platelets leading to platelet activation and aggregation. The possibility of such interactions in the case of viral vector-based vaccines cannot be ruled out and requires further investigation. Furthermore, as shown in Table 1, the findings of negative anti-PF4 antibodies in selective cases indicate involvement of a non-HIT like mechanism hence strengthening the above suggested hypothesis.

Future research should focus on potential interactions between spike

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Table 1 (continued)

| Author | Sex and Age | Past Medical history | Presenting Complaint | Vaccine administered | Laboratory findings | Radiological findings | Intervention | Outcome |
|--------|-------------|----------------------|----------------------|----------------------|---------------------|----------------------|-------------|---------|
| Tarawneh et al. [48] | 22 y/o male | N/A | Petechia and gums bleeding 3 days post-vaccination | Pfizer-BioNTech mRNA | Platelets = 2 × 10^9 | N/A | Dexamethasone 40 mg daily for 4 days, platelet transfusion, and IVIG at 1 g/kg for 2 days | Recovered |

N/A: Not Available, OCP: Oral contraceptives, IVIG: Intravenous Immunoglobulins, ITP: Immune thrombocytopenia, PE: Pulmonary embolism, CVST: Cerebral venous sinus thrombosis, IV: Intravenous, SC: Subcutaneous, PO: Per os LMWH: Low molecular weight heparin, DVT: Deep vein thrombosis.

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Fig. 2. Geographical distribution of the reported cases.
proteins and platelets and the phenomenon of cross-reactivity. Another intriguing aspect of the higher prevalence of VITT among individuals vaccinated with viral vector-based vaccines needs to be investigated in the search for potential links. Development of thrombosis in selective individuals and incidence of rare site thrombosis like cerebral venous sinuses deserve equal attention for the exact pathophysiology to be elucidated. Lastly, the development of anti-PF4 antibodies only in certain VITT patients can also provide important clues in determining the pathogenesis.

1.4. Diagnosis

Following the escalation in reported thrombocytopenia and thrombosis cases post COVID-19 vaccination, the American Society of Hematology (ASH) reviewed all the reported cases and laid specific ground rules to diagnose this novel presentation. As per the ASH [42], cases meeting the following criteria can be identified as VITT:

a) Symptom onset 4–42 days post SARS-CoV-2 vaccination
b) Any venous or arterial thrombosis (often cerebral or abdominal)
c) Thrombocytopenia
d) Antibodies to platelet factor 4 (PF4) identified by enzyme-linked immunosorbent test (ELISA)
e) Markedly elevated D-dimer (>4 times upper limit of normal)

Individuals presenting with the complaints of severe headache, visual changes, abdominal pain, nausea, vomiting, back pain, shortness of breath, leg pain or swelling, petechiae, easy bruising, or bleeding, 4–42 days post-vaccination, must be evaluated critically for the condition mentioned above. Laboratory investigations, including CBC with breath, leg pain or swelling, petechiae, easy bruising, or bleeding, 4–42 days post-vaccination, must be evaluated critically for the condition mentioned above. Laboratory investigations, including CBC, PF4 ELISA, d-dimer, fibrinogen, and imaging techniques for thrombosis, can play a crucial role in timely diagnosis and management [42].

1.5. Management

Currently, numerous potential pharmacological therapies are being evaluated in the line of management for VITT. The outcomes range from being propitious to contraindicated or variable in different individuals. Briefed below are specific interventions being employed to overcome VITT.

1.6. Intravenous Immunoglobulins (IVIG)

The currently available evidence acknowledges IVIG as a potential treatment depicting remarkable success. Hence it is now incorporated into the treatment regimen. A potential explanation for this involves the Fcy receptor blockade by the antibodies. The recommended dose in VITT is 1–2 g/kg of the person’s body weight. However, ideally, the administered IVIG should be the ones collected before the pandemic. The plausible explanation being vaccine response deterioration due to COVID-19 antibodies present in the donated IGs [43].

1.7. Anticoagulants

There has been growing evidence of their efficacy in patients with VITT [44]. In some instances, preliminary trials to validate its effectiveness and progressive clinical worsening in some instances [45] have raised suspicions over its use regarding heparin. Therefore, the American society of hematology (ASH) suggests avoiding the use of heparin unless VITT has been ruled out or another condition diagnosed [42].

The drug of choice is direct oral anticoagulants (dabigatran, apixaban, rivaroxaban, edoxaban, and fondaparinux) or parenteral direct thrombin inhibitors (e.g., bivalirudin and argatroban). The absolute contraindication following anti-coagulation therapy includes a high risk of bleeding. Hence strict clinical monitoring is crucial after initiating oral anticoagulants.

1.8. Steroids

Most cases of VITT described steroids as a clinically effective treatment option. However, further data is needed to move past the anecdotal evidence. The above data and prediction are based on their successfully reported usage in our included cases and recently, by Schultz et al. [46], where the combined IVIG and steroids were supported.

1.9. Platelet infusion

This therapy is only indicated in significant bleeding. Goel et al. [47] reported a five times increase in mortality of patients infused with platelets following thrombocytopenia. In our included studies, eight reportedly administered platelet infusion. Following Goel et al. [47,48], only two patients survived [49].

1.10. Platelet exchange

Plasma exchange was used in three cases. Two out of the three patients survived [50,51]. Relevant details by Garnier et al. were unavailable [14]. Plasma exchange is used in refractory VITT [52]. Clinically, there is insufficient data to evaluate whether plasma exchange can be administered safely in VITT.

Plasma exchange is not a standard treatment option in HIT [42]. Extrapolating this to VITT, we may assume similar effects on patients with VITT. However, more data is required to draw any conclusion.

1.11. Aspirin and rituximab

Aspirin or other anti-platelets are currently contra-indicated in VITT due to increased risk of bleeding. Smith et al. [53] suggested a possible prophylactic role of antiplatelets in VITT. This highlights the need for more work in this area.

Rituximab is not recommended currently due to its longer response time (6–8 weeks) [42]. Moreover, this drug’s mechanism of action can be explained via its downregulation of CD-20 B-cells. This can potentially lead to the inactivation of antibodies against COVID-19, hence rendering the vaccine administration useless.

1.12. Treatment regimen

The following regimen is per the American Society of Hematology (ASH) [42], International Society on Thrombosis and Haemostasis (ISTH) [54], and National Institute for Health and Care Excellence (NICE) in the United Kingdom:

1. Start IVIG.
2. The ISTH guidelines recommend administering steroids if a patient’s platelet count is less than 50 × 10^9/L.
3. Platelet infusion and plasma exchange should not be considered initially.
4. Based on their history and previous clinical profile, patients shall be started an anticoagulant (non-heparin). Vitamin K antagonists should be avoided while the platelet count is low. Moreover, direct thrombin inhibitors should be avoided in pregnant women. DOACs and fondaparinux are suitable for noncritically ill patients.
5. For patients having less than 50 × 103/µL and severe risk of bleeding, IV direct thrombin inhibitors can be used. This will lead to a shorter half-life and rapid action.
6. Fibrinogen levels should be strictly monitored and kept in range (>1.5 g/L)
7. If platelet count remains less than 30 × 10^9/L despite intravenous immunoglobulin and steroid treatment or fibrinogen level is less
than 1 g/L, plasma exchange can be considered after an opinion with hematologists.

2. Conclusion

VITT is a rare adverse effect of SARS-CoV-2 vaccination, and the benefits of COVID-19 vaccines continue to outweigh the rare side effects. However, while its incidence is low, there is undoubted an overwhelming need to discern the precise pathophysiology behind this syndrome to establish proper management protocols. Questions like why certain coronavirus vaccines carry a higher risk than others, why specific individuals develop thrombosis while others don’t, higher prevalence in a particular gender and age group, and the impact of different interventions in such patients need to be investigated before a clear conclusion can be drawn. Lastly, future studies must take into consideration both pre-and post-vaccination investigations to discern the role of any underlying condition.

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Author contribution

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Declaration of competing interest

The authors declare that there is no conflict of interests.

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