***Review Article***

**Thrombocytopenia as an emerging adverse event associated with COVID-19/SARS-CoV2 vaccination**


## Abstract

This review includes data supporting thrombocytopenia as an emerging adverse event associated with SARS-CoV2 vaccination, analyzes the published case reports supporting an association with acquired Thrombotic Thrombocytopenic Purpura(aTTP), reviews the association of Thrombosis with Thrombocytopenia Syndrome(TTS) and Immune Thrombocytopenia Purpura(ITP), analyzes data from the FDA's VAERS database, provides guidance for clinicians caring for patients desiring vaccination but at potential risk of COVID-19 vaccination associated thrombocytopenia, and provides guidance for patients with a history of thrombocytopenia to better enable an informed decision regarding the choice of vaccination. Although the incidence of thrombocytopenia is sufficiently low to allow the continued use of SARS-CoV2 vaccines in patients with a history of thrombocytopenia, caution is advised. The burden of disease in reported patients was significant with death in 8.99% of patients developing thrombocytopenia after receiving the covid vaccine and 15.4% having a life-threatening event. The burden on the healthcare system includes 30.6% of reported patients developing thrombocytopenia after receiving the covid vaccine requiring an ED visit, 26.5% requiring an office visit, and 49.5% requiring hospitalization. Hospitalizations were significant with a median stay of 7.21 days. Patients desiring vaccination should be screened for prior thrombocytopenia and counseled on the risks/benefits of vaccination that are unique to their medical history. Patients with a history of thrombocytopenia may choose to receive vaccination but should be monitored for the development of thrombocytopenia during 0-90 days and possibly as long as nine months following their last dose of vaccination.



Keywords: COVID-19, Vaccine, thrombocytopenia, Thrombotic Thrombocytopenia Purpura, Thrombosis with Thrombocytopenia Syndrome, Immune Thrombocytopenia Purpura

## Introduction

March 2020, COVID-19 was declared a global pandemic due to the highly contagious disease caused by the Severe Acute Respiratory Coronavirus 2 (SAR-CoV-2).[1] It can cause severe morbidity and mortality especially in older patients and patients with chronic preexisting medical diseases. Emerging vaccines were shown to be effective in preventing COVID-19 in clinical trials, and rapid regulatory approval was provided.[2,3] Mass vaccination was initiated in December 2020 to provide immunity against the pandemic. Risks of Adverse Events with COVID vaccination create anxiety among patients and reduced vaccination rates. Thrombocytopenia is emerging as a serious adverse event associated with COVID-19 vaccines. Knowledge of the etiologies of thrombocytopenia occurring with COVID-19 vaccination, the severity of illness, treatment options and outcomes is needed to ensure providers of vaccines are able to identify patients at risk and initiate strategies to ensure patient safety.

## Methods

A literature search using the terms thrombocytopenia and covid vaccine resulted in identifying case reports, case-controlled series, healthcare provider database analyses and opinion articles. The American Society of Hematology COVID-19 Resources were reviewed. The Vaccine Adverse Event Reporting System (VAERS) database was queried from the onset of COVID 19 vaccination use in the United States December 14, 2020 until October 24, 2021. Using these resources, a narrative description of the various etiologies of thrombocytopenia has been created to provide guidance and better enable those recommending and administering COVID-19 vaccination to identify and monitor patients at risk.

## Review

Reports of SARS-CoV-2 vaccination associated thrombocytopenia have been accumulating with groups such as the United States (U.S.) Centers of Disease Control (CDC) and Food and Drug Administration (FDA), and American Society of Hematology accepting etiologies that include Thrombocytopenia Syndrome (TTS) and Immune Thrombocytopenia Purpura (ITP). Included in published case reports are cases due to acquired Thrombotic Thrombocytopenic Purpura (aTTP). In an electronic health record study performed in England, rates of thrombocytopenia in adults aged <70 years were higher 1 to 28 days after ChAdOx1-S (aHR 1.71, 1.35 to 2.16), but not after BNT162b2 (1.00, 0.75 to 1.34) compared with unvaccinated patients.[4] In a Chinese population, the incidence of thrombocytopenia was found to be more common than other hematological abnormalities with thrombocytopenia, leukopenia, and neutropenia incidence of 1.39, 1.17, and 0.26 per 10 000 doses of BNT162b2 vaccine.[5] The occurrence of thrombocytopenia after vaccination does not appear to be increased in Pregnant patients in the U.S.[6]

## Thrombosis with Thrombocytopenia Syndrome (TTS)

Receiving great attention on April 13, 2021 when the U.S. FDA and CDC suggested pausing administration of the AD26.CoV2.S J&J vaccine to allow investigation of several cases of severe thrombosis with thrombocytopenia. Following investigation, description of this syndrome, and provision of management guidance, the FDA and CDC recommended resumed use of this vaccine. Subsequently on December 16, 2021, ACIP held an emergency meeting to review updated data on TTS and an updated benefit-risk assessment. At that meeting, ACIP made a recommendation for preferential use of mRNA COVID-19 vaccines over the Janssen COVID-19 vaccine, including both primary and booster doses administered to prevent COVID-19, for all persons aged ≥18 years. The Janssen COVID-19 vaccine may be considered in some situations, including for persons with a contraindication to receipt of mRNA COVID-19 vaccines.[7]

Thrombocytopenia associated with the Adenovirus vector vaccines, AD26.COV2.S Johnson & Johnson (JJ) vaccine and CHaDOx1 nCov-19 AstraZeneca (AZ) vaccine, have been given several names: "Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT)" or "Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)" but has been termed "Thrombosis with Thrombocytopenia Syndrome (TTS)" by the CDC and FDA.[8] All three terms refer to the same syndrome characterized by venous or arterial thrombosis, commonly involving atypical sites of cerebral sinus venous thrombosis or splanchnic thrombosis, with mild to severe thrombocytopenia, and positive PF4-heparin ELISA antibody. The incidence of TTS in the U.S. is 3.83 per million vaccine doses (Ad26.COV2.S) and 0.00855 per million vaccine doses (mRNA-based COVID-19 vaccines).[9] The initial mortality rates with TTS of 60% have improved to 22% with the development of healthcare provider experience managing this condition.[10] The most common locations of thrombosis are reported as cerebral venous sinus thrombosis, pulmonary embolism, and deep vein thrombosis.[11] However, it appears that overall rate of these events is low in patients receiving the AZ vaccine with a risk difference compared to non-vaccinated individuals of 8.35 per 100,000 for Deep Venous Thrombosis, 1.68 per 100,000 vaccinations for cerebral venous thrombosis, and 2.39 per 100,00 vaccinations for thrombocytopenia.[12] Patients of any age may be affected, and have presented 4 to 42 days following COVID-19 vaccination, with the peak incidence between 6 to 14 days post-vaccination. Patients also typically have markedly elevated D-dimer with values over four times upper limit of normal. This disease can be rapidly fatal and immediate medical evaluation is required. Treatment recommendations are rapidly evolving and currently include avoidance of Heparin, administration of IVIG and non-heparin anticoagulants, and consideration of Plasma exchange.[13] Although the TTS incidence rate with messenger RNA SARS-CoV-2 vaccines is much lower than that associated with adenoviral vector vaccines, there have been case reports describing an association with the mRNA-1273 SARS-CoV-2 Vaccine (Moderna, Inc.).[14]

Although thrombosis has received the most attention, less severe presentations have been described to include purpuric rash.[15] The goal of raising awareness is to encourage healthcare providers to consider TTS in patients presenting with mild symptoms such as isolated thrombocytopenia or thrombocytopenia with purpuric rash and institute treatment prior to the development of a life-threatening thrombotic event.

PF4 antibodies have been found to develop in the post-vaccination patient at a rate of (All: 6.8% [95% confidence interval (CI), 4.4-10.3]; BNT162b2: 5.6% [95% CI, 2.9-10.7]; ChAdOx1

nCoV-19: 8.0% [95% CI, 4.5% to 13.7%]). However, none of the PF4/polyanion EIA+ samples induced platelet activation in the presence of PF4 suggesting that most patients that develop PF4 antibodies do not progress to be clinically relevant.[16]

The PF4-heparin ELISA antibody assay result must be carefully considered. It has been demonstrated that that while Ad26.COV2.S-associated TTS patients are uniform in their strongly positive in PF4-polyanion enzyme-linked immunosorbent assays (ELISAs); they are frequently negative in the serotonin release assay (SRA). This same group reports identification of a novel ELISA assay capable of distinguishing between TTS and Heparin Induced Thrombocytopenia (HIT), spontaneous HIT, and commonly-encountered HIT-suspected patients who are PF4/polyanion ELISA-positive but negative in functional assays.[17]

Although, patients with a history of Heparin Induced Thrombocytopenia (HIT) are considered at an increased risk for symptomatic VITT, this is not a data driven conclusion and in the United Kingdom, 20 of 60 patients with a confirmed history of HIT received the AstraZeneca vaccination with none reporting any features suggestive of VITT.[18] Regardless, the authors continued an initiative to guide patients with a history of HIT away from use the AstraZeneca vaccine.

Patient populations with antiphospholipid antibody associated baseline prevalence of PF4 antibodies without associated thrombocytopenia were found to tolerate COVID-19 vaccination without the development of TTS. This suggests similar patients may safely take the vaccine and there may be no role for PF4 antibody screening in the absence of thrombocytopenia.[19]

The duration of PF4 antibodies and future risk of additional vaccination is of the utmost importance to clinicians but guidance cannot be reliably provided at this time. An observation of 65 patients diagnosed with TTS after receiving an adenoviral vector vaccine has found that 73.8% of patients will become functional assay negative over a range of 5-28 weeks, but sero-reversion to a negative ELISA occurred in only 21.5% of patients. None of the 29 TTS patients who received a second vaccination dose with an mRNA COVID-19 vaccine developed thrombosis, and only two showed a decrease in platelet count with the lowest platelet count suffering a decline from 153 to 111 platelets.[20] A United Kingdom study found the rate of PF4 antibody persistence varied by assay with the Immucor assay having the highest rate of 94% positivity at 20 weeks from symptom onset.[21]

The etiology of COVID-19 vaccines in the development of PF4 antibodies is in the early stages of investigation with consideration of a pathogenic role of vaccine encoded soluble SARS-CoV-2 spike protein.[22] Another possibility is that certain individuals experience a high titer of the negatively charged impurity proteins expressed by the vaccine, e.g., adenovirus skeleton proteins that provoke the creation of PF4 antibodies.[23] There is a difference in the amount of impurities between adenoviral vector vaccines that may contribute to differences in the rate of VITT with Ad26.COV2.S having a much lower amount of impurities found compared to ChAdOx1 nCoV-19 vaccine.[24]

## Acquired Thrombocytopenic Thrombocytopenia (aTTP)

Acquired Thrombocytopenic Thrombocytopenia (aTTP) association with SARS-CoV-2 vaccine is less established but appears present. Prior to COVID-19, an association of aTTP with viral vaccines, particularly influenza vaccine, has been postulated based on case reports.[25] Published cases supporting an association of aTTP with SARS-CoV-2 vaccine are reviewed in Table 1. These cases are notable for the presence of thrombocytopenia and microangiopathic anemia with a diagnosis supported by ADAMTS13 deficiency. Also remarkable for a broad age range from 30-80 years old, occurring both in male and female, with several vaccine manufacturers within 5-37 days of either the 1st or 2nd vaccine dose, and occurring both de novo and as a relapse in patients with a history of TTP. aTTP should be considered in any patient presenting with thrombocytopenia and microangiopathic anemia regardless of the presence of symptoms. It is an immune-mediated disease in which autoantibodies develop against A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), the von Willebrand factor (vWF) cleaving protease. This creates a deficiency of ADAMTS13 activity and results in un-cleaved long vWF-multimers that cause spontaneous platelet aggregates in conditions of high shear and associated thrombosis in small vessels.[26] Due to the thrombotic nature of the disease, when allowed to progress, aTTP patients may develop fever, renal insufficiency, neurological symptoms, cardiac ischemia symptoms, and abdominal pain, but these symptoms need not be present to establish a diagnosis. Although, the referenced case reports are notable for patient survival, this is likely due to rapid identification and treatment initiation as aTTP is rapidly fatal with a mortality greater than 90% when untreated, but boasts a greater than 90% survival when treated with the immediate initiation of plasma exchange. Treatments for aTTP include immediate initiation of Plasmapheresis, with additional benefits from glucocorticoids, rituximab, and caplacizumab. Disease activity may be prolonged with treatment continuation for months, and some patients are susceptible to recurrence both within one-year and many years later.[26]

## Immune Thrombocytopenia Purpura (ITP)

Immune Thrombocytopenia Purpura (ITP) has a larger body of data supporting its association SARS-CoV-2 vaccination. These reports have been noted following the administration of both the Adenovirus vector and mRNA vaccines by the four major manufacturers, Astra Zeneca, Johnson & Johnson, Moderna, and Pfizer. Patients typically present with bleeding, platelet counts of less than 10,000 and an absence of thrombosis. Sufficient cases have been reported to provide an estimated association of 1 in 100,000 to 1 in 1,000,000 patients receiving SARS-CoV-2 vaccination. Reports of mortality are uncommon, and patients have done well by responding to typical first line ITP treatments that includes IVIG and/or glucocorticoids with platelet transfusions as needed to stop bleeding.[13] A case report from outside the U.S. describes a successful outcome following accepted ITP treatments of intravenous immunoglobulin and corticosteroids.[27] While the safety of additional COVID-19 vaccination in patients experiencing ITP with a prior vaccine dose is unclear, a case report has demonstrated that a 73-year-old woman with de novo ITP after a first injection of SARS-Cov-2 mRNA vaccine (Moderna

vaccine) safely tolerated a dose of SARS-Cov-2 mRNA vaccine (Pfizer vaccine) a few months later.[28]

## Miscellaneous

Thrombocytopenia associated with Haemophagocytic lymphohistiocytosis (HLH) has been reported with both adenoviral vector and mRNA COVID-19 vaccines. It is a rare, severe, uncontrolled hyperinflammatory reaction where activated lymphocytes and histiocytes infiltrate all organs and secrete large amounts of cytokines, leading to tissue damage and organ failure. Characteristic features include prolonged fever, splenomegaly, pancytopenia and haemophagocytosis. Biochemical markers include hyperferritinaemia, hypertriglyceridaemia and hypofibrinogenaemia. In the absence of treatment, HLH is uniformly fatal. When diagnosed sufficiently early to initiate treatment, the median survival of patients suffering HLH is 54% with a complex treatment regimen that is beyond the scope of this article and may include steroids, immunosuppressives, anti-neoplastic agents and allogeneic hematopoietic cell transplant. HLH should be considered in patients presenting with thrombocytopenia associated with the appearance of immune activation associated with fever or progressive multi-organ failure within 61 days of any dose of COVID-19 vaccination and an absence of an alternative cause of the syndrome.[29]

Bone marrow suppression was determined to be the cause of thrombocytopenia in a 74-year-old male who developed pancytopenia recorded seven days after receiving the Pfizer SARS-CoV-2 vaccine that improved without specific treatment.[30]

The following published case report cannot be defined as a specific illness and an association cannot be established. A patient suffering myositis, thrombocytopenia, and myocarditis has been reported after receiving Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine. Notable is this syndrome began 12-days after receiving the first dose of vaccine, and resolved after treatment with a 5-day course of intravenous methylprednisolone and intravenous immunoglobulin.[31]

## Vaccine Adverse Event Reporting System (VAERS) database

To better understand the occurrence of Thrombocytopenia in association with COVID-19 vaccines, and its burden on patients and the healthcare system, we queried the VAERS database from the onset of COVID 19 vaccination use in the United States December 14, 2020 until October 24, 2021. The Vaccine Adverse Event Reporting System (VAERS) is a national early warning system for detecting possible safety problems in U.S.-licensed vaccines that is co-managed by the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). The database included a total of 1,260 reported cases of thrombocytopenia occurring after receiving the covid vaccine as of October 24, 2021 when 220,562,831 Americans received at least one dose of covid vaccine[32] for an incidence rate of 6

new cases per million covid-vaccinated persons per year which is higher than the incidence of immune TTP of 3 cases per 1 million persons per year.[33] Analysis of the database demonstrates a strong association of thrombocytopenia with covid vaccine compared to other vaccines with 96.85% of reported thrombocytopenia cases associated with the covid vaccine. (Table 2) Patients had a median age of 59 with a range of 12-101 years old. The median days from vaccination to symptom onset was 26.50 days. (Table 3) The manufacturer of the vaccination was widely distributed between Pfizer, Moderna and Janssen. (Table 4)

The burden of disease in reported patients was significant with death in 8.99% of patients developing thrombocytopenia after receiving the covid vaccine and 15.4% having a life-threatening event. The burden on the healthcare system includes 30.6% of reported patients developing thrombocytopenia after receiving the covid vaccine requiring an ED visit, 26.5% of patients requiring an office visit, and 49.5% requiring hospitalization. Hospitalizations were significant with a median stay of 7.21 days with a range of 1 to 90 days. Notable is this burden is exclusively due to covid vaccine with 97-98% of post-vaccine thrombocytopenia life-threatening events and death occurring in patients receiving a covid vaccine, and 97-98% post-vaccine thrombocytopenia requiring a healthcare visit or hospitalization occurring in patients receiving a covid vaccine. (Table 5)

The VAERS data set has limitations due to its open reporting mechanism. Although healthcare professionals are required to report adverse events and vaccine manufacturers are required to report all events that come to their attention, anyone can report an adverse event to VAERS. In addition, VAERS is a passive reporting system that relies on these individuals to report their experiences to the CDC and FDA without a mechanism to ensure completeness or accuracy of the reported cases or identify unreported cases. In this manner, it collects data on reported adverse events, but is not designed to determine if a vaccine has caused a health problem. With this design, it has been especially useful for detecting unusual or unexpected patterns of adverse events that may suggest an association or possible safety problem with a vaccine. In regards to thrombocytopenia, it provides a signal that there is possibly an association with the COVID-19 vaccine but cannot offer information as to the types of thrombocytopenia that are occurring or determine if the vaccine was the cause of the thrombocytopenia. While it suggests that patients having thrombocytopenia following receipt of the COVID-19 vaccine are at an increased health risk and consume a large amount of healthcare services, it cannot determine if the thrombocytopenia itself is the cause of this decline in their well-being or need for the reported healthcare visits.

## Conclusion

Thrombocytopenia is an emerging adverse event to SARS-CoV2 vaccination. While it has different final pathways, it has been described in association with diseases that are believed to be immune-mediated. Although the incidence is sufficiently low to allow the continued use of SARS-CoV2 vaccines in patients with a history of an immune-mediated thrombocytopenia, caution is advised. Patients desiring vaccination should be screened for prior thrombocytopenia events, and counseled on the risks/benefits of vaccination that are unique to their medical history.

Patients with a history of immune-mediated thrombocytopenia may choose to receive vaccination, but should be monitored closely for the development of thrombocytopenia during 0-90 days and possibly as long as nine months following their last dose of vaccination. At this time, it is reasonable to consider a history of immune-mediated thrombocytopenia or thrombocytopenia associated with a viral targeted vaccine as a medical justification for the patient to decline SARS-CoV2 vaccination.

**References**


1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020;91(1):157-160. doi:10.23750/abm.v91i1.9397

2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

3. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine*. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389

4. Whiteley WN, Ip S, Cooper JA, et al. Association of COVID-19 vaccines ChAdOx1 and BNT162b2 with major venous, arterial, or thrombocytopenic events: A population-based cohort study of 46 million adults in England. *PLoS Med*. 2022;19(2):e1003926. doi:10.1371/journal.pmed.1003926

5. Sing CW, Tang CTL, Chui CSL, et al. COVID-19 vaccines and risks of hematological abnormalities: Nested case-control and self-controlled case series study. *Am J Hematol*. 2022;97(4):470-480. doi:10.1002/ajh.26478

6. Rawal S, Tackett RL, Stone RH, Young HN. COVID-19 Vaccination among Pregnant People in the U.S.: A Systematic Review. *Am J Obstet Gynecol MFM*. Published online March 10, 2022:100616. doi:10.1016/j.ajogmf.2022.100616

7. Oliver SE, Wallace M, See I, et al. Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices - United States, December 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(3):90-95. doi:10.15585/mmwr.mm7103a4

8. Cattaneo M. Thrombosis with Thrombocytopenia Syndrome associated with viral vector COVID-19 vaccines. *Eur J Intern Med*. 2021;89:22-24. doi:10.1016/j.ejim.2021.05.031

9. See I, Lale A, Marquez P, et al. Case Series of Thrombosis With Thrombocytopenia Syndrome After COVID-19 Vaccination-United States, December 2020 to August 2021. *Ann Intern Med*. Published online January 18, 2022. doi:10.7326/M21-4502

10. Uzun G, Pelzl L, Singh A, Bakchoul T. Immune-Mediated Platelet Activation in COVID-19 and Vaccine-Induced Immune Thrombotic Thrombocytopenia. *Front Immunol*. 2022;13:837629. doi:10.3389/fimmu.2022.837629

11. Elberry MH, Abdelgawad HAH, Hamdallah A, et al. A systematic review of vaccine-induced thrombotic thrombocytopenia in individuals who received COVID-19 adenoviral-vector-based vaccines. *J Thromb Thrombolysis*. Published online February 14, 2022. doi:10.1007/s11239-021-02626-w

12. Hviid A, Hansen JV, Thiesson EM, Wohlfahrt J. Association of AZD1222 and BNT162b2 COVID-19 Vaccination With Thromboembolic and Thrombocytopenic Events in Frontline Personnel : A Retrospective Cohort Study. *Ann Intern Med*. Published online February 1, 2022. doi:10.7326/M21-2452

13. Thrombosis with Thrombocytopenia Syndrome - Hematology.org. Accessed January 23, 2022. https://www.hematology.org:443/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

14. Sangli S, Virani A, Cheronis N, et al. Thrombosis With Thrombocytopenia After the Messenger RNA–1273 Vaccine. *Ann Intern Med*. 2021;174(10):1480-1482. doi:10.7326/L21-0244

15. Hung YT, Huang YL, Chang YY, Chen WT. Unilateral linear purpuric rash heralding SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *Journal of the European Academy of Dermatology and Venereology*. n/a(n/a). doi:10.1111/jdv.18014

16. Thiele T, Ulm L, Holtfreter S, et al. Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2. *Blood*. 2021;138(4):299-303. doi:10.1182/blood.2021012217

17. Kanack AJ, Singh B, George G, et al. Persistence of Ad26.COV2.S-associated vaccine-induced immune thrombotic thrombocytopenia (VITT) and specific detection of VITT antibodies. *Am J Hematol*. Published online February 7, 2022. doi:10.1002/ajh.26488

18. Faruqi U, White K, Murray N, Cutler J, Breen K. The impact of COVID-19 vaccination on patients with a history of heparin-induced thrombocytopenia. *British Journal of Haematology*. n/a(n/a). doi:10.1111/bjh.18048

19. Lonati PA, Bodio C, Scavone M, et al. Production of anti-PF4 antibodies in antiphospholipid antibody-positive patients is not affected by COVID-19 vaccination. *RMD Open*. 2022;8(1):e001902. doi:10.1136/rmdopen-2021-001902

20. Schönborn L, Thiele T, Kaderali L, et al. Most Anti-PF4 Antibodies in Vaccine-induced Immune Thrombotic Thrombocytopenia are transient. *Blood*. Published online February 3, 2022:blood.2021014214. doi:10.1182/blood.2021014214

21. Craven B, Lester W, Boyce S, et al. Natural history of PF4 antibodies in vaccine induced immune thrombocytopenia and thrombosis. *Blood*. Published online March 11, 2022. doi:10.1182/blood.2021014684

22. Michele MD, Piscopo P, Crestini A, et al. Vaccine-induced immune thrombotic thrombocytopenia: a possible pathogenetic role of ChAdOx1 nCoV-19 vaccine encoded soluble SARS-CoV-2 spike protein. *Haematologica*. Published online 2020. doi:10.3324/haematol.2021.280180

23. Pang X, Liu H, He X, Ji T, Zhu Y, Cui Y. Potential Anionic Substances Binding to Platelet Factor 4 in Vaccine-Induced Thrombotic Thrombocytopenia of ChAdOx1-S Vaccine for SARS-CoV-2. *Front Immunol*. 2021;12:782335. doi:10.3389/fimmu.2021.782335

24. Michalik S, Siegerist F, Palankar R, et al. Comparative analysis of ChAdOx1 nCoV-19 and Ad26.COV2.S SARS-CoV-2 vector vaccines. *Haematologica*. Published online January 20, 2022. doi:10.3324/haematol.2021.280154

25. Yavaşoğlu İ. Vaccination and Thrombotic Thrombocytopenic Purpura. *Turk J Haematol*. 2020;37(3):218-219. doi:10.4274/tjh.galenos.2020.2020.0060

26. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012;158(3):323-335. doi:10.1111/j.1365-2141.2012.09167.x

27. Lee JH, Oh SM, Lee E, Bang JH, Park SW. Treatment for Immune Thrombocytopenia in Coronavirus Disease 2019 (COVID-19) Infection after COVID-19 Vaccination: A Case Report. *Infect Chemother*. Published online December 20, 2021. doi:10.3947/ic.2021.0072

28. Chanut M, Jaidi R, Kohn M, et al. Successful mRNA SARS-Cov-2 vaccine rechallenge after a first episode of immune thrombocytopenic purpura. *Platelets*. Published online February 28, 2022:1-2. doi:10.1080/09537104.2022.2044463

29. Wu V, Lopez CA, Hines AM, Barrientos JC. Haemophagocytic lymphohistiocytosis following COVID-19 mRNA vaccination. *BMJ Case Rep*. 2022;15(3):e247022. doi:10.1136/bcr-2021-247022

30. Shastri T, Randhawa N, Aly R, Ghouse M. Bone Marrow Suppression Secondary to the COVID-19 Booster Vaccine: A Case Report. *J Blood Med*. 2022;13:69-74. doi:10.2147/JBM.S350290

31. Al-Rasbi S, Al-Maqbali JS, Al-Farsi R, et al. Myocarditis, Pulmonary Hemorrhage, and Extensive Myositis with Rhabdomyolysis 12 Days After First Dose of Pfizer-BioNTech BNT162b2 mRNA COVID-19 Vaccine: A Case Report. *Am J Case Rep*. 2022;23:e934399. doi:10.12659/AJCR.934399

32. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Coronavirus Pandemic (COVID-19). *Our World in Data*. Published online March 5, 2020. Accessed January 23, 2022. https://ourworldindata.org/covid-vaccinations

33. Reese JA, Muthurajah DS, Kremer Hovinga JA, Vesely SK, Terrell DR, George JN. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. *Pediatr Blood Cancer*. 2013;60(10):1676-1682. doi:10.1002/pbc.24612

34. Maayan H, Kirgner I, Gutwein O, et al. Acquired thrombotic thrombocytopenic purpura: A rare disease associated with BNT162b2 vaccine. *J Thromb Haemost*. 2021;19(9):2314-2317. doi:10.1111/jth.15420

35. de Bruijn S, Maes MB, De Waele L, Vanhoorelbeke K, Gadisseur A. First report of a de novo iTTP episode associated with an mRNA-based anti-COVID-19 vaccination. *J Thromb Haemost*. 2021;19(8):2014-2018. doi:10.1111/jth.15418

36. Chamarti K, Dar K, Reddy A, Gundlapalli A, Mourning D, Bajaj K. Thrombotic Thrombocytopenic Purpura Presentation in an Elderly Gentleman Following COVID Vaccine Circumstances. *Cureus*. 2021;13(7):e16619. doi:10.7759/cureus.16619

37. Waqar SHB, Khan AA, Memon S. Thrombotic thrombocytopenic purpura: a new menace after COVID bnt162b2 vaccine. *Int J Hematol*. 2021;114(5):626-629. doi:10.1007/s12185-021-03190-y

38. Sissa C, Al-Khaffaf A, Frattini F, et al. Relapse of thrombotic thrombocytopenic purpura after COVID-19 vaccine. *Transfus Apher Sci*. 2021;60(4):103145. doi:10.1016/j.transci.2021.103145

39. Deucher W, Sukumar S, Cataland SR. Clinical relapse of immune-mediated thrombotic thrombocytopenic purpura following COVID-19 vaccination. *Res Pract Thromb Haemost*. 2022;6(1):e12658. doi:10.1002/rth2.12658

40. Innao V, Urso S, Insalaco M, Borraccino A, Consoli U. Immune Thrombotic Thrombocytopenic Purpura following Pfizer-BioNTech anti-COVID-19 vaccination in a patient healed from lymphoma after allogeneic hematopoietic stem cell transplantation. *Thromb Res*. 2022;210:91-93. doi:10.1016/j.thromres.2021.12.029

41. Yocum A, Simon EL. Thrombotic Thrombocytopenic Purpura after Ad26.COV2-S Vaccination. *Am J Emerg Med*. 2021;49:441.e3-441.e4. doi:10.1016/j.ajem.2021.05.001

| Table 1: Published cases of aTTP associated with SARS-CoV-2 vaccination | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Age | Gender | Manufacturer | Days from vaccination to Symptom onset | de novo vs relapse | Clinical Presentation | ADAMTS13 deficiency | Treatments | reference |
| 40 | female | BNT162b2 | 8 days from 2nd dose | relapse | somnlence, fever, hematuria, ecchymosis | yes | Plasma Exchange, Steroids, caplacizumab | Maayan[34] |
| 40 | male | BNT162b2 | 28 days from 2nd dose | relapse | Dysarthria, chest pain | yes | Plasma Exchange, Steroids, caplacizumab, rituximab | Maayan |
| 31 | female | BNT162b2 | 13 days from 1st dose | de novo | vaginal bleeding, purpura | yes | Plasma Exchange, Steroids, caplacizumab, rituximab | Maayan |
| 30 | male | BNT162b2 | 8 days from 2nd dose | de novo | purpura | yes | Plasma Exchange, Steroids, caplacizumab, rituximab | Maayan |
| 38 | female | BNT162b2 | 14 days from 1st dose | de novo | Bruises, Central Serous chorioretinopathy | yes | Plasma Exchange, Steroids, caplacizumab, rituximab | de Bruijn[35] |
| 80 | male | BNT162b2 | 14 days from 2nd dose | de novo | generalized weakness, malaise | yes | Plasma Exchange, Steroids, rituximab | Chamarti[36] |
| 69 | male | BNT162b2 | 7 days from 2nd dose | de novo | fatigue, dyspnea | yes | Plasma Exchange, Steroids | Waqar[37] |
| 48 | female | BNT162b2 | 6 days from 2nd dose | relapse | ecchymoses | yes | Plasma Exchange, Steroids | Sissa[38] |
| 28 | female | BNT162b2 | 6 days from 1st dose | relapse | Arm bruising | Yes | Steroids, caplacizumab, rituximab | Deucher[39] |
| 33 | female | BNT162b2 | 9day from 1st dose | de novo | asthenia, drowsiness, headache, nausea abdominal pain, purpura | yes | Plasma Exchange Steroids, caplacizumab | Innao[40] |
| 62 | female | ChAdOx1 nCoV-19 | 37 days from dose (1st/2nd unspecified) | de novo | confusion | yes | Plasma Exchange, Steroids | Yocum[41] |

| Table 2: Thrombocytopenia cases in VEARS database | | |
|---|---|---|
| Total count | 1,301 | |
| COVID vaccinated | 1,260 | 96.8486% |

| Table 3: Clinical Presentation | | | |
|---|---|---|---|
| | **Age** | **Vaccination Days to Medical Care** | **Vaccination Days to Symptom Onset** |
| **Median** | 59 | 56.75 | 26.50 |
| **Range** | 12 - 101 | 0 - 274 | 0 - 257 |

| Table 4: Vaccine Manufacturer | |
|---|---|
| **Company** | **Number of Patients** |
| PFIZER\BIONTECH | 611 |
| MODERNA | 432 |
| JANSSEN | 210 |
| UNKNOWN | 7 |

| Table 5: Burden of Adverse Reaction to patients and Healthcare System. | | | | |
|---|---|---|---|---|
| | **From Total Thrombocytopenia Patients** | **From Total Thrombocytopenia + COVID Vaccine Patients** | **VARIANCE Thrombocytopenia & COVID Vaccine** | **TOTAL Thrombocytopenia + COVID Vaccine** |
| Died | 119 | 117 | 98.3193% | 8.9931% |
| Life threatening | 206 | 201 | 97.5728% | 15.4497% |
| ER visit | 405 | 398 | 98.2716% | 30.5919% |
| Office visit | 354 | 345 | 97.4576% | 26.5181% |
| Hospitalized | 660 | 644 | 97.5758% | 49.5004% |
| In-patient (>=1 day) | 393 | 386 | 98.2188% | 29.6695% |
| Median (days) | 7.18 | 7.21 | | |
| Range (days) | 1 - 90 | 1 - 90 | | |