Asian Journal of Research in Infectious Diseases

Volume 15, Issue 10, Page 47-57, 2024; Article no.AJRID.120728
ISSN: 2582-3221

COVID-19 and Pulmonary Embolism: A Comprehensive Review of Epidemiology, Pathophysiology, and Management

Uzma Tahniyath [a++*], Deepika V [b#], Maheshwari S [b#] and Alekhya M [b#]

[a] Department of Pharmaceutical Analysis and Quality Assurance, St. Pauls College of Pharmacy, Hyderabad, Turkayamjal, India.
[b] St. Pauls College of Pharmacy, Hyderabad Turkayamjal, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajrid/2024/v15i10381

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/120728

Review Article

Received: 08/07/2024
Accepted: 12/09/2024
Published: 16/09/2024

ABSTRACT

Global public health has suffered greatly as a result of the coronavirus illness 2019 (Covid-19) pandemic; yet when vaccinations against Covid-19 are available, they have contributed to the containment of the spread of SARS Coronavirus 2 (SARS-CoV-2) infection. However, there have been isolated reports of vaccine-induced cerebral venous sinus thrombosis (CVST) and vaccine-

---

[++] Assistant professor;
[#] Pharm.D III year;
**Corresponding author: E-mail: ameenuzma154@gmail.com;*

Cite as: *Uzma Tahniyath, Deepika V, Maheshwari S, and Alekhya M. 2024. "COVID-19 and Pulmonary Embolism: A Comprehensive Review of Epidemiology, Pathophysiology, and Management". Asian Journal of Research in Infectious Diseases 15 (10):47-57. https://doi.org/10.9734/ajrid/2024/v15i10381.*

induced immune thrombotic thrombocytopenia (VITT) following viral vector vaccinations (Ad26.COV2 vaccine, AdOx1 nCoV-19 vaccine).One of the most effective ways to address the global health issue as the new SARS-CoV-2 virus spreads around the world is immunization against COVID-19.This condition manifests as thrombocytopenia, the formation of an autoantibody against platelet-factor 4,and widespread thrombosis in unusual places, mainly in the cerebral venous. (PF4). The human Freia receptor on platelets can be bound by the PF4 autoantibody, which can then cause the platelets to aggregate. This is an uncommon side effect that closely mimics the clinical presentation of the traditional immune-mediated HIT illness that develops after heparin exposure. We will talk about the recently reported side effect known as vaccine-induced immune thrombotic thrombocytopenia (VITT),which can happen after receiving specific COVID-19 vaccinations, in this Spotlight. Since the vaccinations have been employed, questions have been raised about their safety. Following the COVID-19 vaccine, the most frequent side effects include local reactions at the injection site and general systemic symptoms like fever, headache, weariness, and myalgia. These side effects could appear shortly after immunization and go away quickly. Nonetheless, a few uncommon cases of vaccine-induced immune thrombotic thrombocytopenia (VITT) have been documented, mostly in relation to vaccinations utilizing viral vectors. Platelet expression of spike protein and subsequent immune response, platelet expression of other adenoviral proteins and subsequent reactions, the role of antibodies against platelet factor 4 (PF4), the direct interaction between adenoviral vector and platelets, the cross-reactivity of antibodies against SARS-CoV-2 spike protein with PF4, the cross-reactivity of anti-adenovirus antibodies and PF4 interaction between spike protein and platelets. Because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can activate platelets, thrombocytopenia while rare in the first presentation may also be an indicator of the severity of the disease. The spike protein-angiotensin converting enzyme 2 (ACE2) connection causes this directly, and the activation of coagulation and inflammation causes it indirectly. In COVID-19, dysregulation of the innate and adaptive immune systems is a significant contributing factor to thrombosis and thrombocytopenia.

Keywords: COVID 19; thrombotic thrombocytopenia; SARS; CVST; ACE 2.

1. INTRODUCTION

Globally, the COVID-19 pandemic has been linked to higher rates of morbidity and mortality, making it a significant public health concern [1].The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was not significantly treated by any of the experimental and currently available antiviral medications [1].As of this writing, the European Union has authorized four vaccines: two that were created using the mRNA platform (mRNA-1273 by Modern, Cambridge, MA, USA and BNT162b by Biotech/Pfizer, Germany, Mainz/New York, NY, USA) and two that were created using vector vaccines based on modified, replication-deficient (E1/E3-deletion) adenoviruses (AZD1222, ChAdOx1 nCov-19 by Oxford/AstraZeneca, UK/Sweden, and Ad26.COV2.S by Janssen/Johnson Johnson, Leiden, Netherlands/New Brunswick, NJ, USA) [2].The results of the clinical trials have demonstrated a high safety profile, with the primary sources of reactogenicity being short-term local (such as pain, redness, or swelling at the injection site) and systemic (such as headache, fever, or weariness) responses [3].Vaccine-induced thrombotic thrombocytopenia (VITT) is the term used to describe cases of thrombosis consistent with thrombocytopenia that have been discovered after vaccination with Ad26.COV2.S or ChadOx1 nCoV-19·Auto [4] antibodies against the platelet factor 4 (PF-4) antigen, which are comparable to those found in individuals with autoimmune heparin-induced thrombocytopenia (HIT), have been connected to a number of these cases [5]. As far as we are aware, Agostino et al. [6] released the first of these case reports on April 8th. Numerous further reports were released shortly after. Furthermore, reports of occurrences have also been made with the Ad26.COV2. S vaccine; See et al.'s article was the first to do so [7,8]. Although thrombosis can also occur extrapulmonary, the lung microvasculature is the first site of thrombus formation in COVID-19 damage. The hallmarks of VITT/TTS are thrombosing in the cerebral venous sinuses and splanchnic veins (portal and mesenteric); however, COVID-19 also increases the prevalence of these uncommon thromboses [9]. Anti-PF4 antibodies may indicate elevated PF4, which may be implicated in thrombogenesis even though they may not directly cause thrombosis. In addition to platelet activation,

PF4's physiological functions include binding to heparin sulphate and neutralizing the vascular endothelium's antithrombogenicity. It has also been demonstrated that PF4 neutralizes heparin [10]. By attaching to bacteria's polyamines, PF4 further enhances the bactericidal action and helps the host identify [11]. Although the exact mechanism underlying VITT remains unknown, parallels with both spontaneous HIT syndrome and heparin-induced thrombocytopenia (HIT) have been proposed [12]. The purpose of this review is to assess the currently suggested mechanisms and offer a possible course of action for diagnosis and treatment [13].

2. METHODOLOGY

Early in 2020,the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic swept over the world, having a significant negative impact on both human health and the economy. This was linked to a sharp rise in research papers about the coronavirus disease 2019 (COVID-19) in an effort to quickly clarify its natural history and pinpoint diagnostic and treatment options [14,15].One of the four successive research steps that might lead to poorly conducted studies is the selection of a research topic that is pertinent to patient care, followed by the quality of the research design, the publication's suitability, and the quality of the research reports. Moreover, randomized controlled trials (RCTs) are the strongest type of evidence used in evidence-based medicine, whereas case series and case reports are the weakest [16]. the methodological quality of COVID-19 studies stratified by geographic regions, journal impact factor, and median time to acceptance, and the methodological quality of COVID-19 research utilizing known quality tools and checklists. a comparison between matched controls and the methodological quality of COVID-19. Here, we demonstrate the correlation between worse methodological quality scores and COVID-19 publications [17] When more compelling information becomes available, COVID-19 clinical trials ought to be reexamine [18].

Purpura thrombocytopenic thrombocytopenia: SARS-related thrombotic thrombocytopenic purpura the thrombogenic consequences of CoV-2 infection are becoming more well acknowledged as a major source of morbidity and mortality in COVID-19 patients who are severely ill. Multifactorial in nature, the so-called "Covid-19 Coagulopathy" is caused by a maladaptive hyper-immuno-inflammatory response and severe endotheliosis produced by a new virus. This inflammatory assault triggers the activation of several complement pathways and a cross-talk in complement coagulation, resulting in the production of this hypercoagulable state and its hazardous consequences that have a negative impact on the result [19,20]. In addition to COVID-19 coagulopathy, certain rare and susceptible individuals may also have COVID-19 thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP), and haemolytic uremic syndrome (a HUS which are rare but serious thrombotic illnesses caused by this particular virus. A combination of thrombocytopenia, microangiopathic haemolytic anaemia, and widespread clot formation in the microvasculature characterizes these two disorders [21].

COVID-19: The coronavirus-induced sickness begins with respiratory, sneezing, or cough droplets from an infected person and manifests as an immunological response in two to fourteen days. Symptoms include: Fever, cough, dyspnoea, exhaustion, chills, occasionally accompanied by trembling; body aches; diarrhoea, vomiting; headache; sore throat; congestion or runny nose; loss of taste or smell [22]. The virus spreads along the respiratory system. hates the airways, which comprise the lungs, nose, throat, and mouth. Compared to the remainder of the respiratory tract, the lower airways have more ACE2 receptors. Therefore, compared to viruses like the common cold, COVID-19 is more likely to spread. Breathing may become difficult due to inflammation of the lungs [23]. Pneumonia may result from an infection of the alveoli, which are tiny sacs inside the lungs where oxygen and carbon dioxide exchange occurs. Acute respiratory distress syndrome, immune system disorders, heart problems, blood vessel problems, brain disorders, liver problems, eye problems, and kidney damage may also be brought on by this. It's still unknown how COVID-19 will affect our bodies in the long run [24,25].

Thrombosis: Thrombosis mechanisms — In addition to triggering platelets and coagulation,anti-PF4 antibodies also trigger "pan cellular" activation, which means that they stimulate neutrophils, which results in enosis, monocytes, and endothelial cells, which results in tissue factor expression. The elevated risk of thrombosis is further increased by the activation

of these additional cell types [26]. A characteristic of VITT is thrombosis in unusual sites such as the splanchnic (splenic, portal, mesenteric) veins, adrenal veins (risk for adrenal failure), cerebral and ophthalmic veins. Thrombosis in VITT can also occur in typical sites of venous thromboembolism, such as pulmonary embolism or deep vein thrombosis (DVT) in the leg. There have also been cases of arterial thrombosis, which include peripheral arterial occlusion and ischemic stroke (often involving the middle cerebral artery), frequently in people who also have concurrent venous thrombosis [27]. Unknown is the pathophysiologic reason for these peculiar thrombosis sites. The distribution is comparable to other uncommon thrombophilia's including myeloproliferative neoplasms and paroxysmal nocturnal haemoglobinuria (PNH). Numerous large and small veins are involved in catastrophic venous thrombosis, as autopsy studies on VITT-related deaths have shown [28].

Vaccine induced thrombotic thrombocytopenia: Although the exact mechanism underlying VITT remains unknown, parallels with both spontaneous HIT syndrome and heparin-induced thrombocytopenia (HIT) have been proposed. The purpose of this study is to assess the currently suggested mechanisms and offer a possible course of action for diagnosis and treatment. Qualities of VITT antibodies consist of the IgG class.

- Identify PF4 attached to platelets; the PF4 epitope is distinct from the epitope identified by antibodies causing heparin-induced thrombocytopenia (HIT).
- Not heparin-dependent (not induced by heparin exposure; do not require heparin for detection in in vitro platelet activation assays).
- Detectable in PF4/polyanion and PF4 enzyme-linked immunosorbent assay (ELISA) and in functional assays.
- Cause platelet activation.

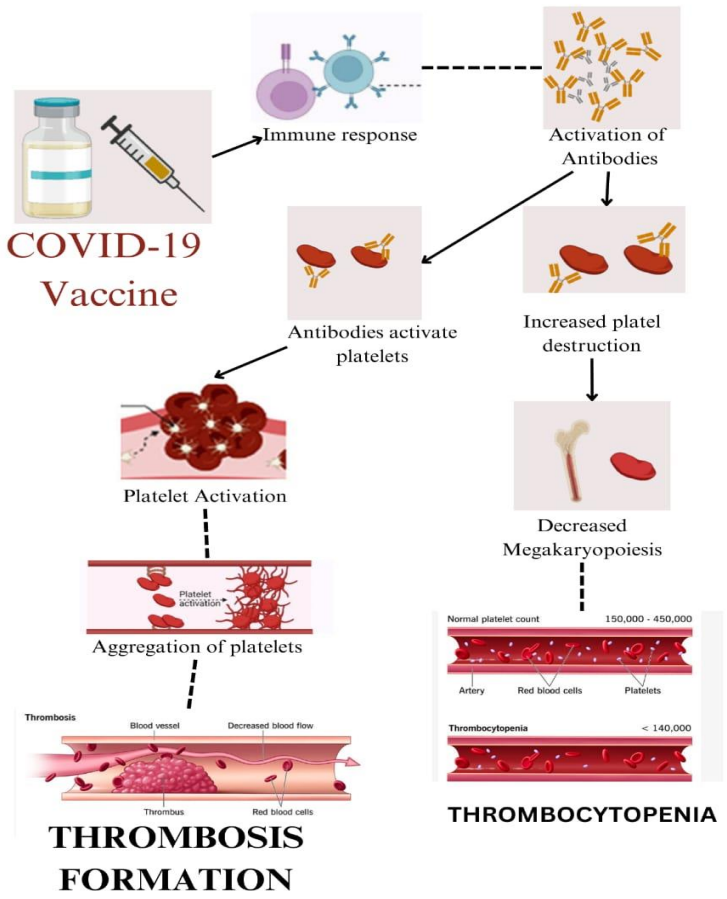

Fig. 1. COVID 19 vaccine induced TTP

Compared to HIT antibodies, which are usually heparin-dependent,this is a significant distinction. Heparin inhibited platelet binding and platelet aggregation with patient sera, according to in vitro research. It is unknown what this means clinically, however one study found that the production of procoagulant indicators in an in vitro experiment was heparin-dependent [29]. Heparin treatment for VITT is changing. Thrombocytopenia and thrombosis at unusual sites, such as the cerebral vein, portal vein, splanchnic vein, and hepatic vein, along with a tendency towards haemorrhagic transformation, are the hallmarks of VITT.It reacts to non-heparin anticoagulants and IVIG steroids [30].

Covid -19-induced TTP: Due to the existence of an ADAMTS-13 blocking antibody in circulation, the second condition is a de novo COVID-19 caused immunological TTP; immunosuppressants and plasma exchange (PEX) are required for both syndromes. Thus far in this epidemic, over twenty cases of de novo it has been documented.Through a potentially unique mechanism or even the unmasking of an occult one, their ethology has been directly linked to SARS CoV-2 infection. This has resulted in the emergence of an inhibitor of this protease, a significant decrease in ADAM TS-13 activity,and a severe TMA.PEX and immunosuppressants had an effect on these patients [31]. In addition to these, two further TTP syndromes have also been identified.First, there has been recent report of an uncommon and complex overlap TTP syndrome associated with COVID-19.A single dosage of anti CD20 monoclonal antibody rituximab appears to have altered the course of an underlying resistive condition in this complex syndrome (intolerance prohibiting its subsequent dosing).A superadded COVID-19 infection resulted in a distinct TTP phenotype with overlapping TTP characteristics, such as sickness and it.The COVID-19 vaccine exposure-related therapy-related it, which requires PEX and immunosuppression, further broadens the spectrum. It can cause either a de novo or known relapse of the illness due to a novel mechanism (molecular mimicry by the spike antigen and an amplified T cell and B cell response) [32].It is important to distinguish between vaccine-induced immunity (VI-it) and another recently identified uncommon thrombotic condition, the vaccine-induced immune after being exposed to ChAdOx1 nCoV-19 (Astra Zeneca), thrombotic thrombocytopenia (VITT) occurred, adding another disease to the growing list of thrombotic sequelae linked to COVID-19.The latter condition lacks a history of previous heparin exposure and is instead an HIT (heparin-induced thrombocytopenia)-like sickness brought on by vaccination-induced development of antibodies against the platelet factor 4 (PF4) polyanion complex [33].

Diagnosis:

Treatment: A cautious and well-coordinated strategy is necessary to treat a patient with both COVID-19 and thrombotic thrombocytopenic purpura (TTP), addressing both disorders at the same time.The important therapeutic factors are as follows:

COVID-19 treatment:

1. **Antiviral Therapies:** Remdesivir is one medication that can be used to lessen the length and severity of an infection.
2. **Monoclonal antibodies:** These are utilized, especially in high-risk individuals, for early outpatient treatment to prevent severe disease.
3. **Anti-inflammatory Drugs:** In extreme circumstances, dexamethasone or other corticosteroids are used to lessen inflammation.

TTP treatment:

1. **Plasma Exchange (PEX):** To eliminate autoantibodies and restore ADAMTS13 enzyme levels, plasma exchange is the cornerstone of TTP treatment.
2. **Corticosteroids:** Prednisone is one of the steroids used to inhibit the immune system and lessen inflammation.
3. **Rituximab:** This monoclonal antibody is used in refractory or relapsing instances; it targets B cells.
4. **Caplacizumab:** This antibody against the von Willebrand factor (vWF) is used to stop the development of microthrombi.

Combined treatment approach:

1. Anticoagulation: TTP and COVID-19 both raise the risk of thrombosis. Anticoagulation needs to be carefully controlled to balance the risk of bleeding and thrombosis.
2. Immunomodulation: To prevent aggravating COVID-19, immuno suppressive medication may need to be

adjusted, particularly if steroids or rituximab are being used.

3. Multidisciplinary Care: To properly manage these illnesses, coordination between critical care physicians,infectious disease specialists and haematologists is essential.
4. A customized treatment regimen is necessary for each patient, taking into account the severity of COVID-19 and TTP as well as any other underlying medical disorders [34].

3. RESULTS

Up until the end of November 2021, twenty cases of iTTP following COVID-19 vaccination have been reported, in addition to our case. The cases consisted of 10 female and 11 male individuals, with a median age of 50 years (range 14–84 years) at diagnosis. There were five individuals (24%) who had a history of iTTP. Eighty-one percent used mRNA-based vaccinations, while nineteen percent used recombinant adenoviral vector-based vaccines. Twenty individuals showed symptoms within 30 days following the vaccine, with a median onset of symptoms of 12 days (range 5–37).For every patient, therapeutic plasma exchange was a part of the treatment. 43% (9/21) of cases received further rituximab, 14% (3/21) received additional rituximab, and 24%(5/21)of cases received additional treatment [35].At the conclusion of the observational period, all of the surviving patients were in clinical remission, although one patient had a prolonged clinical course.Vaccine-induced thrombotic immune thrombocytopenia (VITT)is one of the differential diagnoses for immune-thrombocytopenia post-SARS-CoV-2 immunization [36,37].The clinical presentation of VITT appears 5–30 days following the first dose of adenoviral-based COVID-19 vaccinations and is similar to spontaneous autoimmune heparin-induced thrombocytopenia (HIT).Patients diagnosed with VITT often present with arterial or venous thrombosis,deep venous thrombosis, and pulmonary embolism, often at atypical sites such as cerebral sinus veins, splanchnic, and portal veins [38,39]. Patients may also have moderate-to-severe thrombocytopenia.Acute iTTP episodes typically manifest as diffuse microvascular thrombosis, significant haemolysis, and severe thrombocytopenia (<30 G/L).Auto-antibodies against ADAMTS13 are formed in iTTP patients, and these antibodies either accelerate the clearance of ADAMTS13 or block its action, resulting in a severe ADAMTS13 deficit.Anti-platelet factor (PF) 4/heparin antibodies are present in VITT patients [40,41] and ADAMTS13 activity, if detected,is either normal or just slightly decreased [42,43]. The initial mortality rate of 40–50% has decreased to less than 25% as a result of growing VITT awareness, early diagnosis, and effective treatment.

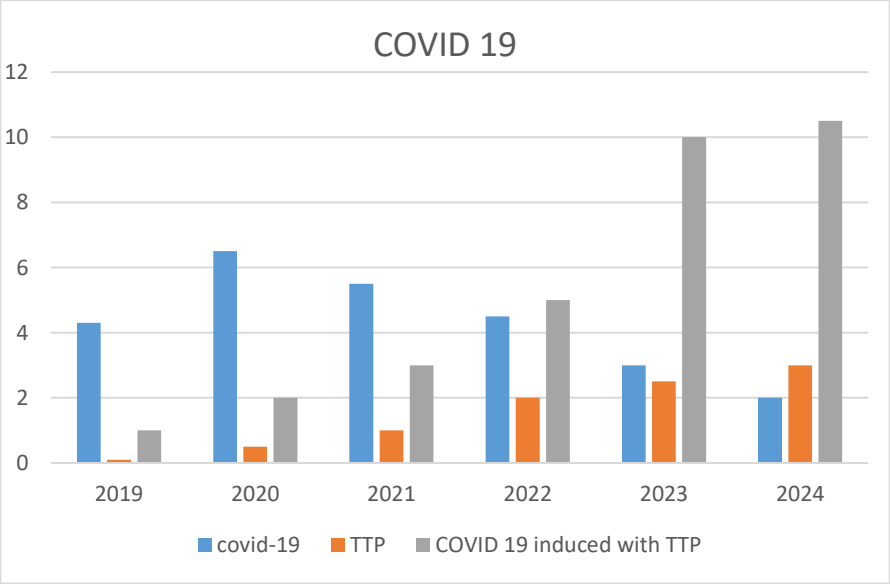

Fig. 2. COVID 19 induced with TTP in different years

Within a 10-month period, 21% of the cases in our cohort of newly diagnosed aTTP cases had a history of immunization with Sars-CoV-250.Nonetheless, under our nationwide system of vigilance for adverse events, no additional instance of aTTP following immunization was reported during the duration of our trial.The yearly incidence of aTTP previously reported in our region (0.2 per million) increased to an average of 17 new episodes each year (0.377 per million) between January 2017 and July 2022, according to our department's diagnosis data Here,we report 19 newly diagnosed cases of aTTP, which is marginally more than this norm, and was diagnosed between January and October 2021 [44,45].

4. DISCUSSION

The idea of TTP after immunization is not brand-new. Following vaccination against influenza, pneumococcal disease,H1N1,and rabies,there have been isolated reports of TTP.These were typically observed two weeks after immunization and in conjunction with vaccinations against viral agents.Since COVID-19 vaccines were developed quickly due to an urgent necessity, monitoring these immune systems has become more complex even with our current understanding of them Following COVID-19 vaccination, autoimmune reactions such as VITT,Miller-Fisher syndrome, Guillain-Barre syndrome, and ITP have been identified. Similar to VITT(thrombocytopenia and thrombosis with neurological changes),TTP can mimic its symptoms, delaying diagnosis and treatment [46]. This becomes especially problematic when it comes to starting PLEX which is thought of as a second-line treatment for VITT as opposed to TTP,where it is typically the first modality administered to save lives [47]. Because of this, evaluating post-vaccine thrombocytopenia presents a serious diagnostic challenge.Given the fatality associated with this condition and the urgency of treatment, physicians must take into account the possibility of TTP, as the mortality risk of TTP without early therapy remains high at 80–90%. After vaccination, the pathophysiology of de-novo TTP is still unclear, according to two schools of thinking. One theory describes the possibility that people with symptoms beginning within a few days of receiving the vaccine may have undiagnosed occult TTP that manifests as a complete episode following a trigger (vaccine) [48]. A second idea is that autoantibodies against ADAMTS13 could develop by molecular mimicking pathways subsequent to an immune trigger. Furthermore, there is evidence to suggest that an acute recurrence in patients with recurrent acquired or congenital TTP cannot be caused solely by an ADAMTS13 deficit.A "second hit" in the form of inflammation or infection is necessary to cause acute TTP, and in these circumstances, it was thought to be these cases was considered to be the COVID-19 vaccine [14]. It has previously been proposed that immune cross-reactivity between vaccine components and self-proteins, which results in the production of autoantibodies anti-ADAMTS13, may occur after influenza/H1N1,9-11 pneumococcal,12 or rabies13immunization.This idea, however, is unlikely to be supported by the temporal correlation shown in our study and in the literature between the injection of the vaccination and the start of the first symptoms in certain recorded cases [45,48]. With rates of 0.195 per million in the United States 8 and 0.118 per million in France, they demonstrated that the incidence of de novo or relapse aTTP did not rise with the administration of the COVID-19 vaccine,taking into account only cases occurring within 30 days of immunization. Furthermore, recent literature research revealed no cross-reactivity between autoantibodies to SARS-CoV-2 S1 Spike protein binding and ADAMTS13.This may provide a better explanation for why TMA symptoms occurred in a few patients soon after vaccination. The importance of tracking the vaccine response in individuals with a history of acquired or congenital TTP has been highlighted [19], even though no more research supports either theory [49,50].

5. CONCLUSION

Thrombotic thrombocytopenic purpura (TTP) is one of the consequences linked to the COVID-19 pandemic. Tiny clots forming in blood vessels are the hallmark of TTP,an uncommon blood illness that can cause haemolytic anaemia,low platelet counts,and even organ damage. Significant morbidity and mortality are linked to TTP related with the Covid-19 vaccination. For this reason, in patients presenting with thrombocytopenia following COVID-19 vaccination, prompt diagnosis and treatment are crucial. For TTP, plasma exchange along with steroids is the standard of care. With insufficient response,early rituximab and alacizumab beginning should be taken into consideration. Although the advantages of the COVID-19 immunization significantly outweigh the risks, it is important to recognize that TTP could have a negative

outcome.To assess the association between COVID-19 vaccines and TTP,more investigation is required.This includes comparing the epitope profiles of COVID-19 vaccine antigens with ADAMTS-13 and determining the predictive criteria for the development of TTP following COVID-19 immunization.Ninety-nine million vaccine recipients from ten locations spread over eight nations participated in the Global Vaccine Data Network cohort study. For thirteen medical disorders connected to the nervous system, blood, and heart, researchers compared the observed and expected rates.This is the first report of aTTP cases following BBIBP- CorV or Gam- COVID-Vac administration.These vaccinations are in addition to those that have previously been documented in the literature as initiating anti-ADAMTS13 autoimmunity.In the context of uncommon diseases,the prevalence may appear to be very low,yet awareness of these potential events should be widely disseminated in order to appropriately diagnose patients and treat them quickly.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT ANDD ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Julia V Magalhaes, Ronald LG Flumignan, Vinicius T Civile, Carolina DQ Flumignan, Mateus AB Cristino, Marcello E Reicher, Luis CU Nakano. Pharmacological treatments for vaccine-induced immune thrombocytopenia and thrombosis (VITT) after COVID-19 vaccination. The Cochrane Database of Systematic Reviews. 2024; (2):2024.
2. Perspectives on vaccine induced thrombotic thrombocytopenia Arad Dotan, Yehuda Shoenfeld Journal of Autoimmunity. 2021;121:102663.
3. Amin Islam, Mohammed Sheraz Bashir, Kevin Joyce, Harunor Rashid, Ismail Laher, Shereen Elshazly. An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations. Molecules. 2021;26(16):5004.
4. Ismail Elalamy, Grigoris Gerotziafas, Sonia Alamowitch, Jean-Pierre Laroche, Patrick Van Dreden,Walter Ageno, Jan Beyer-Westendorf, Alexander T Cohen, David Jimenez, Benjamin Brenner,Saskia Middeldorp, Patrice Cacoub. SARS-CoV-2 vaccine and thrombosis: An expert consensus on vaccine-induced immune thrombotic thrombocytopenia Scientific Reviewer Committee Thrombosis and haemostasis. 2021;121(08):982-991.
5. Maryam Sharifian-Dorche, Mohammad Bahmanyar, Amirhossein Sharifian-Dorche, Pegah Mohammadi, Masood Nomovi, Ashkan Mowla. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; A systematic review. Journal of the Neurological Sciences. 2021;428;117607.
6. Toshiaki Iba, Jerrold H Levy. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends in Cardiovascular Medicine. 2022;32(5):249-256.
7. Mostafa H Elberry, Hussien Ahmed H Abdelgawad, Aboalmagd Hamdallah, Walid Shaban Abdella, Ahmed Sayed Ahmed, Hazem S Ghaith, Ahmed Negida. A systematic review of vaccine-induced thrombotic thrombocytopenia in individuals who received COVID-19 adenoviral-vector-based vaccines. Journal of Thrombosis and Thrombolysis. 2022;53(4):798-823.
8. Aashish Gupta, Partha Sardar, Michael E Cash, Richard V Milani. COVID-19 vaccine-induced thrombosis and thrombocytopenia-a commentary on an important and practical clinical dilemma. Carl J Lavie Progress in Cardiovascular Diseases. 2021;67:105.
9. Richard G Jung, Pietro Di Santo, Cole Clifford, Graeme Prosperi-Porta, tephanie Skanes, Annie Hung,Simon Parlow, Sarah Visintini,F Daniel Ramirez,Trevor Simard,Benjamin Hibbert. Methodological quality of COVID-19 clinical research.

Nature Communications. 2021;12(1): 943.

10. Mohammad Alhomoud, Tamara Alhobayb, Keith Armitage. COVID-19 infection triggering thrombotic thrombocytopenic purpura. IDCases. 2021;26:e01256.
11. Dimitrios Tsilingiris, Natalia G Vallianou,Irene Karampela,Maria Dalamaga. Vaccine induced thrombotic thrombocytopenia: The shady chapter of a success story. Metabolism Open. 2021;11: 100101.
12. Tajamul H Mir. COVID-19 associated divergent thrombotic thrombocytopenic purpura (TTP) syndromes reported so far, five and counting: Classification and possible therapeutic options.
13. Marija Malgaj Vrecko, Department of Nephrology, University Medical Center Ljubljana,1000 Ljubljana,Slovenia. Coronavirus Disease 2019-Associated Thrombotic Microangiopathy Marija Malgaj Vreckoa,b, c , Zeljka Veceric-Halera, baDepartment of Nephrology, University Medical Center Ljubljana, 1000 Ljubljana, Slovenia bFaculty of Medicine, University of Ljubljana.
14. Thrombotic thrombocytopenic purpura (TTP) after COVID-19 vaccination: A systematic review of reported cases Prachi Saluja,a Nitesh Gautam,a Sisira Yadala,b and Anand N. Venkatac.
15. James McFadyen, Angela Huang, Sanjeev Chunilal, Vivien Chen, Huyen Tran. Understanding vaccine-induced thrombotic thrombocytopenia (VITT) Caroline Dix. Internal Medicine Journal. 2022;52(5):717-723.
16. Alexander Muacevic, John R Adler Chitramalya Dan, Akshat Sahai, Deepmalya Dan, Anmol Sahai, Ram Trehan. Thrombotic thrombocytopenic purpura following pfizer-biontech COVID-19 Vaccination in a patient with multiple myeloma: Case report and literature review monitoring editor.
17. Amin Islam, Mohammed Sheraz Bashir, Kevin Joyce, Harunor Rashid, Ismail Laher, Shereen Elshazly. An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations. Molecules. 2021;26(16):5004.
18. Covid-19: Two rare vaccine side effects detected in large global study. BMJ. 2024;384. DOI: https://doi.org/10.1136/bmj.q488 (Published 26 February 2024)
19. Syed Hassan Ahmed, Taha Gul Shaikh, Summaiyya Waseem, Nashwa Abdul Qadir, Zohaib Yousaf, Irfan Ullah. Vaccine-induced thrombotic thrombocytopenia following coronavirus vaccine: A narrative review. Annals of Medicine and Surgery. 2022;73:102988.
20. Paul Elias Alexander, Victoria Borg Debono, Manoj J Mammen, Alfonso Iorio, Komal Aryal, Dianna Deng, Eva Brocard, Waleed Alhazzani. COVID-19 coronavirus research has overall low methodological quality thus far: Case in point for chloroquine/hydroxychloroquine. Journal of Clinical Epidemiology. 2020;123:120-126.
21. An evaluation of the quality and impact of the global research response to the COVID-19 pandemic.
22. Meng-zhu Zhao, Chen Zhao, Shuang-shuang Tu, Xu-xu Wei, Hong-cai Shang. Evaluating the methodology of studies conducted during the global COVID-19 pandemic: A systematic review of randomized controlled trials. Journal of Integrative Medicine. 2021;19(4):317-326.
23. Sergio Bonini. COVID-19 Clinical trials: Quality matters more than quantity. Giuseppe Maltese Allergy. 2020;75(10): 2542-2547.
24. Mahir Fidahic, Danijela Nujic, Renata Runjic, Marta Civljak, Filipa Markotic, Zvjezdana Lovric Makaric, Livia Puljak. Research methodology and characteristics of journal articles with original data, preprint articles and registered clinical trial protocols about COVID-19. BMC Medical Research Methodology. 2020;20:1-9.
25. The methodological quality is insufficient in clinical practice guidelines in the context of COVID-19: systematic review.
26. Beatrice Mainoli, Tiago Machado, Gonçalo S Duarte, Luísa Prada, Nilza Gonçalves, Joaquim J Ferreira, João Costa. Analysis of clinical and methodological characteristics of early COVID-19 treatment clinical trials:so much work, so many lost opportunities. BMC Medical Research Methodology. 2021;21:1-10.
27. Brijesh Sathian, Mohammad Asim, Indrajit Banerjee, Ana Beatriz Pizarro, Bedanta Roy, Edwin R Van Teijlingen, Israel Júnior Borges do Nascimento, Hanadi Khamis

Alhamad. Impact of COVID-19 on clinical trials and clinical research: A systematic review. Nepal Journal of Epidemiology. 2020;10(3):878.

28. James B Bussel. SARS-CoV-2 vaccine–induced immune thrombotic thrombocytopenia Douglas B Cines. New England Journal of Medicine. 2021; 384(23):2254-2256.
29. Katharina Guetl, Thomas Gary, Reinhard B Raggam, Johannes Schmid, Albert Wölfler, Marianne Brodmann. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia treated with immunoglobulin and argatroban. The Lancet. 2021;397(10293):e19.
30. Dennis McGonagle, Gabriele De Marco, Charles Bridgewood. Mechanisms of immunothrombosis in vaccine-induced thrombotic thrombocytopenia (VITT) compared to natural SARS-CoV-2 infection. Journal of Autoimmunity. 2021; 121:102662.
31. Ismail Elalamy, Grigoris Gerotziafas, Sonia Alamowitch, Jean-Pierre Laroche, Patrick Van Dreden, Walter Ageno, Jan Beyer-Westendorf, Alexander T Cohen, David Jimenez, Benjamin Brenner, Saskia Middeldorp, Patrice Cacoub. SARS-CoV-2 vaccine and thrombosis: An expert consensus on vaccine-induced immune thrombotic thrombocytopenia. Scientific Reviewer Committee Thrombosis and Haemostasis. 2021;121(08).
32. Nancy Guirguis, Tyler Rehman, Yara Shams, Melanie Gordon, Essam Mekhaiel, Shaina Rozell, Mauna. SARS-CoV-2 infection inducing immune thrombocytopenic purpura: Case series. Pandya Ochsner Journal. 2021;21(2):187-189.
33. Mayte Sánchez Van Kammen, Diana Aguiar De Sousa, Sven Poli, Charlotte Cordonnier, Mirjam R Heldner et al. Characteristics and outcomes of patients with cerebral venous sinus thrombosis in SARS-CoV-2 vaccine–induced immune thrombotic thrombocytopenia.
34. Karina Althaus, Peter Möller, Günalp Uzun, Anurag Singh, Annika Beck, Martin Bettag, Hans Bösmüller, Martina Guthoff et al. Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia. Tamam Bakchoul Haematologica. 2021; 106(8):2170.
35. Malay Sarkar, Irappa V Madabhavi, Pham Nguyen Quy, Manjunath B Govindagoudar COVID-19 vaccine-induced immune thrombotic thrombocytopenia: A review. Annals of Thoracic Medicine. 2022;17(1):1-13.
36. Amin Islam, Mohammed Sheraz Bashir, Kevin Joyce, Harunor Rashid, Ismail Laher, Shereen Elshazly. An update on COVID-19 vaccine induced thrombotic thrombocytopenia syndrome and some management recommendations. Molecules. 2021;26(16):5004.
37. Ariunzaya Amgalan, Maha Othman. Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions. Journal of Thrombosis and Haemostasis. 2020;18(6): 1514-1516.
38. Toshiaki Iba, Jerrold H Levy. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends in Cardiovascular Medicine. 2022;32(5):249-256.
39. Brit Long, Rachel Bridwell, Michael Gottlieb. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines. The American Journal of Emergency Medicine. 2021; 49:58-61.
40. Richard C Becker. COVID-19 update: COVID-19-associated coagulopathy. Journal of thrombosis and thrombolysis. 2020;50(1):54-67.
41. Tajamul H Mir. COVID-19 associated divergent thrombotic thrombocytopenic purpura (TTP) syndromes reported so far, five and counting: Classification and possible therapeutic options. Thrombosis Research. 2022;219:86.
42. Jose Ramos-Rojas, Javiera Pena, Carlos Pinto-Diaz, Valentina Veloso, Gabriel Rada, Helvert Felipe Molina-Leon. Thrombotic and thromboembolic events, with or without thrombocytopenia, following viral vector-based COVID-19 vaccines administration: A systematic review protocol. Medrxiv. 2024;0222: 24303207.
43. Peyvandi F, Scully M, Kremer Hovinga JA, Knöbl P et al. Caplacizumab reduces the frequency of major thromboembolic events, exacerbations and death in patients with acquired thrombotic thrombocytopenic purpura. Journal of Thrombosis and Haemostasis. 2017; 15(7):1448-1452.

44. Agnès Ribes, Fanny Vardon-Bounes, Vincent Mémier, Michael Poette, Jonathan Au-Duong, Cédric Garcia, Vincent Minville, Pierre Sié, Alessandra Bura-Rivière, Sophie Voisin. Thromboembolic events and COVID-19. Bernard Payrastre Advances in Biological Regulation. 2020; 77:100735.
45. Cinzia Solinas,Luca Saba,Paolo Sganzerla, Fausto Petrelli. Venous and arterial thromboembolic events with immune checkpoint inhibitors: A systematic review. Thrombosis Research. 2020;196: 444-453.
46. De Roquetaillade, BG Chousterman, D Tomasoni, M Zeitouni, E Houdart, A Guedon, P Reiner, R Bordier, E Gayat, G Montalescot, M Metra, A Mebazaa. Unusual arterial thrombotic events in COVID-19 patients C. International Journal of Cardiology. 2021;323:281-284.
47. Marie-Claude Beaulieu, Danny Sebastien Mettelus, Benjamin Rioux-Massé, Michèle Mahone. Thrombotic thrombocytopenic purpura as the initial presentation of COVID-19. Journal of Thrombosis and Haemostasis. 2021;19(4):1132-1134.
48. Gaetano Giuffrida, Uros Markovic, Annalisa Condorelli, Marianna Calagna, Stephanie Grasso, Andrea Duminuco, Carla Riccobene, Angelo Curto Pelle, Guido Zanghi, Francesco Di Raimondo. Relapse of immune-mediated thrombotic thrombocytopenic purpura following mRNA COVID-19 vaccination: A prospective cohort study. Haematologica. 2022; 107(11):2661.
49. Daniel Sawler, Arabesque Parker, Joanne Britto, M Dawn Goodyear, Haowei L. Time from suspected thrombotic thrombocytopenic purpura to initiation of plasma exchange and impact on survival: A 10-year provincial retrospective cohort study. Sun Thrombosis Research. 2020; 193:53-59.
50. Senthil Sukumar, Bernhard Lämmle, Spero R. Thrombotic thrombocytopenic purpura: Pathophysiology, diagnosis, and management. Cataland Journal of Clinical Medicine. 2021;10(3):536.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of the publisher and/or the editor(s). This publisher and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

© Copyright (2024): Author(s). The licensee is the journal publisher. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/120728