Thrombotic Disorders and COVID-19 Vaccines

Subjects: Medicine, General & Internal

Contributor: Metodija Sekulovski, Niya Mileva, Georgi Vasilev Vasilev, Dimitrina Miteva, Milena Gulinac, Monika Peshevska-Sekulovska, Lyubomir Chervenkov, Hristiana Batselova, Georgi Hristov Vasilev, Latchezar Tomov, Snezhina Lazova, Dobrin Vassilev, Tsvetelina Velikova

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected hundreds of millions worldwide, leading to nearly 7 million deaths globally, although now declared not a worldwide concern anymore. Strenuous research and analysis of various vaccine advances led to the development of multiple COVID-19 vaccines in less than a year from the pandemic's beginning. Different types of vaccines, such as mRNA vaccines, DNA vaccines, viral vector vaccines, and inactivated virus vaccines have been approved and have shown a high degree of efficacy with variable protective levels of up to 95% (70–95% range) in vaccinated individuals against COVID-19.

Keywords: blood disorders ; blood coagulation ; thrombophilia ; hemophilia ; thrombotic incidents ; thrombotic events ; cerebral venous thrombosis

1. Inherited Blood Coagulation Disorders and COVID-19 Vaccines

Coagulopathic hemorrhagic diatheses (coagulopathies) are conditions caused by a congenital or acquired defect in the blood coagulation system. Hemorrhagic diathesis represents an increased tendency to bleed. Hereditary bleeding disorders may occur due to defective platelet function, and, depending upon the predominant functional abnormality, inherited disorders are classified into the three most common groups: defective platelet adhesion, defective platelet aggregation, and disorders of platelet release reaction [1][2].

Most inherited coagulation disorders are induced by qualitative and quantitative defects in a single coagulation factor. Two of the most common factors that are reported are the sex (X)-linked disorders—classic hemophilia or hemophilia A (factor VIII deficiency) and hemophilia B or Christmas disease (factor IX deficiency). Another common and related coagulation disorder is von Willebrand's disease (defect of von Willebrand's factor).

Hemophilia A is the second most common coagulation disorder, next to von Willebrand's disease. It is inherited in an X-linked recessive pattern. Therefore, females are carriers, whereas the disease manifests clinically in males. The frequency of this type of disorder varies in different races, with the highest incidence being in British populations, particularly in royal blood descendants and some European royal families. These patients suffer from bleeding involving any organ for hours or days after injury, and the severity of bleeding correlates with plasma level factor VIII activity. Broadly, the most severe, non-lethal changes in Hemophilia A result from intra-articular hemorrhages that lead to deforming arthrosis. On the other hand, even minor traumas, such as tooth extraction, can lead to massive, life-threatening bleeding in these subsets of patients [3][4][5].

Since COVID-19 is associated with coagulation and thrombotic disorders, little was known about the infection's impact on the clinical outcomes of patients with hemophilia. A retrospective study by Mericliler et Narayan with 1758 adult male patients reported that COVID-19 did not increase the mortality of COVID-19 in hemophilia A patients but increased the risk of bleeding and hospitalizations [6].

WHO and The World Federation of Hemophilia (WFH) guidelines recommend that patients with hemophilia preferably receive subcutaneous vaccination; the problem comes from the fact that the vaccine for COVID-19, as well as most vaccines, is only allowed for intramuscular administration. Bleeding following the administration of an intramuscular vaccine in hemophiliacs is challenging to control. It may require several days, even weeks, of treatment with a clotting factor [7]. These precautions are also valid for patients on anticoagulants or antiplatelets [8].

However, there are some reports of patients with acquired hemophilia A following COVID-19 vaccination [9][10][11][12][13][14][15]. Duminuco et al. described this rare coagulopathy associated with hemorrhagic complications due to the possible

development of FVIII inhibitors following an immune stimulus [9].

Von Willebrand's disease (Pseudohemophilia) has an autosomal dominant inheritance. In this disease, impaired platelet aggregation is detected. Its incidence is estimated to be 1 in 1000 of either sex. Clinically, the patients are characterized by spontaneous bleeding from mucous membranes and excessive wound bleeding [16][17].

As expected, the von Willebrand factor plays a role in COVID-19-associated coagulopathy, as its levels and activity increase in severe infection [18]. However, little to no information is available on COVID-19's impact on patients with this disease [19].

Hemophilia B (Christmas disease) is rarer than hemophilia A, with clinical features indistinguishable from classic hemophilia [20]. Not much is known about COVID-19 in these patients. However, managing underlying hemophilia of any type requires hemostatic treatment for ambulatory patients and prevention with concentrates intensified according to the risk of complications in hospitalized patients and those on replacement therapy [21].

2. Congenital Coagulation and Thrombotic Disorders and COVID-19 Vaccines

Thrombophilia is a type of hypercoagulability that represents a pathologic state of increased clot formation without active bleeding [22].

Factor V Leiden mutation is the most common inherited thrombophilia in individuals with venous thromboembolism. The mutation leads to enhanced pro-thrombotic actions of activated factor Va by changing the cleavage site of the molecule and hindering its degradation by protein C. It is an autosomal dominant genetic condition with incomplete penetrance, so not every carrier of the mutated gene will exhibit a thrombotic event [23].

Protein C and S deficiency: Protein C is a vitamin K-dependent protease presented in low levels in human plasma. Once activated, it cleaves the activated factors V and VIII, thus inhibiting thrombin production and coagulation. The functions of protein C in inflammation and cytoprotection have been described unrelated to its role in coagulation. Protein S is a cofactor to activate protein C in the cleavage of Va and VIIIa, as well as a cofactor of the tissue factor pathway inhibitor (TFPI) [24]. Protein C and S deficiencies may be inherited and acquired. There are two types of inherited forms, most commonly with autosomal recessive inheritance. Type I is associated with decreased levels and activity of the proteins, while type II is related to normal levels but reduced anticoagulant activity. Both protein C and S deficiencies are associated with uncontrolled thrombin formation and thromboembolic events, with venous thromboembolism being more common than arterial [25].

Antithrombin III deficiency: Antithrombin III is a glycoprotein located on the vascular surface of endothelial cells that requires heparin as a cofactor with which they bind circulating thrombin, thus inhibiting coagulation. Antithrombin III deficiency is inherited in an autosomal dominant manner and presents almost exclusively with venous thrombosis. The risk of thrombotic events is higher than in protein S and C deficiencies. Antithrombin III deficiency is estimated to carry the highest venous thromboembolism risk among all hereditary thrombophilias [26].

Hyperhomocysteinemia: Hyperhomocysteinemia has been notorious for decades for causing widespread accelerated atherosclerosis and arterial thrombosis. Homocysteine is an amino acid produced in methionine metabolism that causes endothelial injury and oxidative stress when present in substantial amounts. For homocysteine to be resynthesized to methionine by the enzyme methionine synthase, a methyl group is needed in the form of methyl-tetrahydrofolate delivered by the methylenetetrahydrofolate reductase (MTHFR). Several polymorphisms of the MTHFR gene are associated with significantly elevated serum homocysteine levels, with the homozygous mutant genotype leading to the greatest homocysteine values [27].

A large observational study from the Mayo Clinic, Rochester, Minnesota, USA, identified 6067 patients with confirmed thrombophilia among almost 800,000 vaccinated patients against COVID-19. Subgroup analysis did not find any statistically significant difference in the occurrence of venous thromboembolism between patients with and without thrombophilia vaccinated against COVID-19 [28].

It has even been estimated that the absolute risk for a deep vein thrombosis while undergoing an airplane flight is 1 in 4600 people, making it 50 to 100 times more likely than thrombosis following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination [29]. A European expert consensus on Vaccine-Induced Immune Thrombotic

Thrombocytopenia recommends against the systematic screening for thrombophilia; against premedication with low-molecular-weight heparin, direct oral anticoagulants, or aspirin; as well as against monitoring of changes in D-dimer [29].

3. Blood Coagulation and Thrombotic Disorders Related to COVID-19 Disease

The variety of clinical symptoms associated with novel coronavirus infection astounded researchers. The condition can be asymptomatic, with only modest signs such as olfactory loss, overall weakness, or flu-like symptoms. However, COVID-19 infection can be severe in some patients, resulting in hypercoagulation, vascular endothelial damage, and the risk of venous and arterial thrombotic consequences [30]. Multiple research publications covering various features and signs of the disease have been published in recent months. They reported that the endothelial cells in COVID-19 play a pivotal role as mediators of the two-way communication between inflammation and coagulation [31]. On one hand, SARS-CoV-2 binding to the endothelial angiotensin-converting enzyme 2 receptor activates endothelial cells through a complicated, inflammatory response [32].

On the other hand, studies using COVID-19-infected lung tissue have also shown enhanced expression of vascular and inflammatory factors. These factors include vascular cell adhesion molecule (VCAM)-1, interleukin (IL)-8, and monocyte-chemoattractant protein (MCP)-1. Furthermore, scientific research has proven that platelet adhesion molecule vWF is upregulated in COVID-19, demonstrating endothelial involvement; however, a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), which cleaves high-molecular-weight vWF, is downregulated, resulting in an aberrant ratio of vWF to ADAMTS-13 [33]. This disturbed ratio is at the base of the pathogenesis of COVID-19-associated coagulopathy.

In line with this, it is unsurprising that severe disease and subsequent cardiovascular consequences after SARS-CoV-2 infection are higher in patients with preexisting vascular disease, such as hypertension, diabetes, and coronary artery disease. Since the lungs are the entryway for most viruses and SARS-CoV-2, the pulmonary vasculature is the first to experience inflammation. Barrier function and vascular tone may also be indirectly affected by microvascular thrombosis. Vascular dysfunction and microvascular thrombosis contribute significantly to further developing pulmonary illness, particularly ARDS. There have been reports of increased thrombotic events such as venous thromboembolism, myocardial infarction, and stroke [34].

Although SARS-CoV-2 infection, which causes coronavirus illness (COVID-19), has been linked to thrombotic problems in adults, the prevalence of COVID-19-related thrombosis in children and adolescents is unknown. Mild disease is typical for children with acute COVID-19, but the postinfectious complication known as multisystem inflammatory syndrome in children (MIS-C) has mostly been linked to coagulopathy [35]. Evidence demonstrated that MIS-C and other post-COVID-19 complications may originate in vascular dysfunction. For example, since April 2020, previously healthy children have presented with fever, cardiovascular shock and/or Kawasaki disease symptoms, hyperinflammation, and multisystem involvement after SARS-CoV-2 infection [36]. Many of them had positive SARS-CoV-2 antibody titers but negative nasopharyngeal swabs. Thus, CDC and WHO public health advisories listed criteria for this new disease, a multisystem inflammatory syndrome in children (MIS-C) associated with coagulopathy, as a potential presenting feature [36][37][38].

Therefore, it is essential to underline that immobile patients with severe infection and those with severe inflammatory reactions have an elevated risk of VTE, a key issue for all hospitalized patients. Consequently, preventative measures, including pharmaceuticals and mechanical devices, should be employed, and early mobilization should be encouraged. Since pharmaceutical thromboprophylaxis has been demonstrated to benefit hospitalized patients with COVID-19, a higher dose of anticoagulation may be necessary to treat the severe coagulopathy associated with this virus. In an effort to strike a better balance between thrombotic and bleeding events, it was proposed early on in the pandemic that the dose of thromboprophylaxis be established to empirical therapeutic-dose anticoagulation or to intermediate-dose anticoagulation [39]. Thus, only thromboembolic problems warrant therapeutic-dose heparin in critically ill COVID-19 patients. All patients can prevent VTE with LMWH in prophylactic doses. Some ICU specialists favor unfractionated heparin infusion for VTE in renal failure (ideally guided by anti-factor Xa levels since the aPTT is inaccurate in COVID-19 patients due to excessive factor VIII levels). Heparin-induced thrombocytopenia patients could benefit from fondaparinux, argatroban, or bivalirudin [40]. However, with the growing incidence of bleeding reports associated with COVID-19, several articles recommend using anticoagulation with serious percussion and individually assessing the benefit/risk ratio because of their adverse effects (i.e., paradoxical bleeding during DIC evolution).

With respect to the prognosis, important indicators of poor outcomes in SARS-CoV-2 infections include markers of endothelial dysfunction and altered endothelial cell integrity, which are linked to pulmonary edema, intravascular

thrombosis, and acute respiratory distress syndrome (ARDS). The pulmonary endothelium is critical in maintaining vascular homeostasis and permeability, regulating inflammatory responses, coagulation, and fibrinolysis [41]. Disturbances in these tightly controlled processes may directly lead to morbidity and death.

References

1. Andrikovics, H.; Klein, I.; Bors, A.; Nemes, L.; Marosi, A.; Varadi, A.; Tordai, A. Analysis of large structural changes of the factor VIII gene, involving intron 1 and 22, in severe hemophilia A. Haematologica 2003, 88, 778–784.
2. Rossaint, R.; Afshari, A.; Bouillon, B.; Cerny, V.; Cimpoesu, D.; Curry, N.; Duranteau, J.; Filipescu, D.; Grottke, O.; Grønlykke, L.; et al. The European guideline on management of major bleeding and coagulopathy following trauma: Sixth edition. Crit. Care 2023, 27, 80.
3. Salen, P.; Babiker, H.M. Hemophilia A. In StatPearls ; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK470265/ (accessed on 15 August 2023).
4. Konkle, B.A.; Nakaya Fletcher, S. Hemophilia A. In GeneReviews® ; Adam, M.P., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Gripp, K.W., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.
5. Angelini, D.; Konkle, B.A.; Sood, S.L. Aging among persons with hemophilia: Contemporary concerns. Semin. Hematol. 2016, 53, 35–39.
6. Mericliler, M.; Narayan, G. Outcomes of COVID-19 in Adult Males with Hemophilia A: A Propensity Score-Matched Analysis. Cureus 2022, 14, e30662.
7. Tiede, A.; Leise, H.; Horneff, S.; Oldenburg, J.; Halimeh, S.; Heller, C.; Königs, C.; Holstein, K.; Pfrepper, C. Safety of intramuscular COVID-19 vaccination in patients with haemophilia. Haemophilia 2022, 28, 687–693.
8. Velikov, T.; Keremidchiev, G.; Velikova, T. How to use Safely COVID-19 Vaccines in Patients on Anticoagulants or Antiaggregants. Int. J. Preven Cardio. 2021, 1, 32–33.
9. Duminuco, A.; Calagna, M.; Markovic, U.; Esposito, B.; Grasso, S.; Riccobene, C.; Di Raimondo, F.; Giuffrida, G. Acquired hemophilia A following COVID-19 vaccination—The importance of prompt diagnosis: A case report. Transfus. Apher. Sci. 2023, 62, 103577.
10. Al Hennawi, H.; Al Masri, M.K.; Bakir, M.; Albarazi, M.; Jazaeri, F.; Almasri, T.N.; Shoura, S.J.; Barakeh, A.R.R.; Taftafa, A.; Khan, M.K.; et al. Acquired Hemophilia A Post-COVID-19 Vaccination: A Case Report and Review. Cureus 2022, 14, e21909.
11. Happaerts, M.; Vanassche, T. Acquired hemophilia following COVID-19 vaccination: Case report and review of literature. Res. Pract. Thromb. Haemost. 2022, 6, e12785.
12. Emna, B.; Kmira, Z.; Hajer, B.I.; Nadia, S.; Yossra, D.; Amina, B.; Yosra, B.Y.; Haifa, R.; Abderrahim, K. Acquired hemophilia A following COVID-19 vaccine: A case report. J. Med. Case Rep. 2023, 17, 125.
13. Ai Vuen, L.; Aun Su-Yin, E.; Naila Kori, A.; Shah, T.M. Case of acquired haemophilia a in Southeast Asia following COVID-19 vaccine. BMJ Case Rep. CP 2022, 15, e246922.
14. Hosoi, H.; Tane, M.; Kosako, H.; Ibe, M.; Takeyama, M.; Murata, S.; Mushino, T.; Sonoki, T. Acute-type acquired hemophilia A after COVID-19 mRNA vaccine administration: A new disease entity? J. Autoimmun. 2022, 133, 102915.
15. Radwi, M.; Farsi, S. A case report of acquired hemophilia following COVID-19 vaccine. J. Thromb. Haemost. 2021, 19, 1515–1518.
16. Goodeve, A.; James, P. von Willebrand Disease. In GeneReviews® ; Adam, M.P., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Gripp, K.W., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.
17. Michiels, J.J.; van Vliet, H.H.; Berneman, Z.; Gadisseur, A.; van der Planken, M.; Schroyens, W.; van der Velden, A.; Budde, U. Intravenous DDAVP and factor VIII-von Willebrand factor concentrate for the treatment and prophylaxis of bleedings in patients With von Willebrand disease type 1, 2 and 3. Clin. Appl. Thromb. Hemost. 2007, 13, 14–34.
18. Mei, Z.W.; van Wijk, X.M.R.; Pham, H.P.; Marin, M.J. Role of von Willebrand Factor in COVID-19 Associated Coagulopathy. J. Appl. Lab. Med. 2021, 6, 1305–1315.
19. NHF President and CEO Leonard Valentino, MD, Discusses the Role of von Willebrand Factor (VWF) in Severe Cases of COVID-19. Available online: https://www.hemophilia.org/news/covid-19-and-vwf (accessed on 15 August 2023).
20. Konkle, B.A.; Nakaya Fletcher, S. Hemophilia B. In GeneReviews® ; Adam, M.P., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Gripp, K.W., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.

21. Pipe, S.W.; Kaczmarek, R.; Srivastava, A.; Pierce, G.F.; Makris, M.; Hermans, C.; Interim Guidance; Coagulation Products Safety, Supply and Access (CPSSA) Committee of the World Federation of Hemophilia. Management of COVID-19-associated coagulopathy in persons with haemophilia. Haemophilia 2021, 27, 41–48.
22. Dautaj, A.; Krasi, G.; Bushati, V.; Precone, V.; Gheza, M.; Fioretti, F.; Sartori, M.; Costantini, A.; Benedetti, S.; Bertelli, M. Hereditary thrombophilia. Acta Biomed. 2019, 90, 44–46.
23. Thorelli, E.; Kaufman, R.J.; Dahlbäck, B. Cleavage of factor V at Arg 506 by activated protein C and the expression of anticoagulant activity of factor V. Blood 1999, 93, 2552–2558.
24. Padda, I.S.; Patel, P.; Citla Sridhar, D. Protein C and S. In StatPearls ; StatPearls Publishing: Treasure Island, FL, USA, 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK557814/ (accessed on 15 August 2023).
25. Kate, M.K.; van der Meer, J. Protein S deficiency: A clinical perspective. Haemophilia 2008, 14, 1222–1228.
26. Nakashima, M.O.; Rogers, H.J. Hypercoagulable states: An algorithmic approach to laboratory testing and update on monitoring of direct oral anticoagulants. Blood Res. 2014, 49, 85–94.
27. Park, W.C.; Chang, J.H. Clinical Implications of Methylenetetrahydrofolate Reductase Mutations and Plasma Homocysteine Levels in Patients with Thromboembolic Occlusion. Vasc. Spec. Int. 2014, 30, 113–119.
28. Houghton, D.E.; Wysokinski, W.E.; Padrnos, L.J.; Shah, S.; Wysokinska, E.; Pruthi, R.; Ghorbanzadeh, A.; Ashrani, A.; Sridharan, M.; McBane, R.D.; et al. Venous thromboembolism after COVID-19 vaccination in patients with thrombophilia. Am. J. Hematol. 2023, 98, 566–570.
29. Elalamy, I.; Gerotziafas, G.; Alamowitch, S.; Laroche, J.P.; Van Dreden, P.; Ageno, W.; Beyer-Westendorf, J.; Cohen, A.T.; Jimenez, D.; Brenner, B.; et al. SARS-CoV-2 Vaccine and Thrombosis: An Expert Consensus on Vaccine-Induced Immune Thrombotic Thrombocytopenia. Thromb. Haemost. 2021, 121, 982–991.
30. Bílková, S.; Hirmerová, J. Coagulopathy associated with COVID-19. Koagulopatie asociovaná s onemocněním COVID-19. Vnitr. Lek. 2020, 66, 402–408.
31. Ackermann, M.; Verleden, S.E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F.; Vanstapel, A.; Werlein, C.; Stark, H.; Tzankov, A.; et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N. Engl. J. Med. 2020, 383, 120–128.
32. Shaw, R.J.; Bradbury, C.; Abrams, S.T.; Wang, G.; Toh, C.H. COVID-19 and immunothrombosis: Emerging understanding and clinical management. Br. J. Haematol. 2021, 194, 518–529.
33. Ward, S.E.; Fogarty, H.; Karampini, E.; Lavin, M.; Schneppenheim, S.; Dittmer, R.; Morrin, H.; Glavey, S.; Ni Cheallaigh, C.; Bergin, C.; et al. ADAMTS13 regulation of VWF multimer distribution in severe COVID-19. J. Thromb. Haemost. 2021, 19, 1914–1921.
34. Flaumenhaft, R.; Enjyoji, K.; Schmaier, A.A. Vasculopathy in COVID-19. Blood 2022, 140, 222–235.
35. Whitworth, H.; Sartain, S.E.; Kumar, R.; Armstrong, K.; Ballester, L.; Betensky, M.; Cohen, C.T.; Diaz, R.; Diorio, C.; Goldenberg, N.A.; et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. Blood 2021, 138, 190–198.
36. Riphagen, S.; Gomez, X.; Gonzalez-Martinez, C.; Wilkinson, N.; Theocharis, P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020, 395, 1607–1608.
37. Lazova, S.; Gerenska, D.; Slabakova, Y.; Velikova, T. Immunological features of the multisystem inflammatory syndrome associated with SARS-CoV-2 in children. Am. J. Clin. Exp. Immunol. 2022, 11, 64–71.
38. Lazova, S.; Dimitrova, Y.; Hristova, D.; Tzotcheva, I.; Velikova, T. Cellular, Antibody and Cytokine Pathways in Children with Acute SARS-CoV-2 Infection and MIS-C-Can We Match the Puzzle? Antibodies 2022, 11, 25.
39. Flaczyk, A.; Rosovsky, R.P.; Reed, C.T.; Bankhead-Kendall, B.K.; Bittner, E.A.; Chang, M.G. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: Implications for clinical practice and future investigations. Crit. Care 2020, 24, 559.
40. Cuker, A.; Tseng, E.K.; Nieuwlaat, R.; Angchaisuksiri, P.; Blair, C.; Dane, K.; Davila, J.; DeSancho, M.T.; Diuguid, D.L.; Griffin, D.O.; et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021, 5, 872–888.
41. Klok, F.A.; Kruip, M.; van der Meer, N.J.M.; Arbous, M.S.; Gommers, D.; Kant, K.M.; Kaptein, F.H.J.; van Paassen, J.; Stals, M.A.M.; Huisman, M.V.; et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb. Res. 2020, 191, 148–150.