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(REVIEW ARTICLE)

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A mini-review on the side-effects of COVID-19 vaccines on Thrombosis with Thrombocytopenia Syndrome (TTS)

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Abstract

In May 2024, the well-known pharmaceutical company AstraZeneca admitted that its COVID - 19 (SARS-CoV-2) vaccine can cause the rare side effect of Thrombosis with Thrombocytopenia Syndrome (TTS), involving blood clots along with a low platelet count. This is a potentially severe condition, with a fatality rate up to 44%. Several studies indicate a link between different COVID-19 vaccines and TTS or VITT (Vaccine Induced Thrombotic Thrombocytopenia), however, a majority of such cases have been reported after the vaccines ChAdOx1 nCoV-19, manufactured by AstraZeneca and Oxford University, and Ad26.COV2.S, made by Johnson and Johnson. Both these vaccines use the same mechanism: modified adenovirus vectors. In these viral vector vaccines, some researchers have theorized that an immune response could be triggered where the body produces antibodies against platelet factor 4 (PF4), a protein involved in blood clotting. Another theory suspects endothelial cells and receptors to have an inflammatory response, causing VITT. Though the exact cause remains unknown, an association between some vaccines and thrombotic events can definitely be discerned by past research, so this article will evaluate different vaccines and their connections with such events.

Keywords: SARS-CoV-2; COVID-19 Vaccine; Thrombosis; Thrombocytopenia Syndrome (TTS)

1. Introduction

In late 2019, the pandemic COVID-19 suddenly caused unexpected changes to medicine and research. The strain causing the pandemic was SARS-CoV-2, which quickly spread worldwide, irreversibly damaging society. The novel coronavirus was first recognized in December 2019, after which the publication of the genome took place in early January of 2020, which set the stage for scientific research and countermeasures [1]. Within about 6 months, the virus had already resulted in 380,000 deaths [2]. To date, over 700 million COVID-19 cases have been reported (2024) by the WHO, with many people infected by the virus ending up needing hospital care, estimates suggesting that around 20% of COVID-19 patients required hospitalization [3,4]. Additionally, the virus has resulted in a substantial number of fatalities - as recorded in 2020, during the peak of cases, the mortality rate was 17.1% [5]. This sparked the need to develop preventive measures as soon as possible.

Astonishingly, quite a few COVID-19 vaccines were developed within only 12 months [6]. By June 2020, the demand to prevent COVID-19 remarkably led to the development of 124 vaccine candidates. Among these candidates, 10 had progressed to the critical stages of clinical trials, specifically phase 1 or phase 2 [2]. These phases are essential to assess the safety and immunogenicity of the vaccines in humans. Within this group of 10 vaccine candidates, there was considerable skepticism regarding their potential for efficient large-scale production. The complexities of manufacturing vaccines at such an unprecedented scale involve technology, infrastructure, raw materials, production facilities, and skilled personnel. There were doubts about the substantial efficacies of these vaccine candidates. Efficacy,

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which refers to the ability of the vaccine to provide protection against the virus, is a critical factor that determines the overall success of a vaccination campaign. Variations in immune response among different demographic groups, potential mutations in the virus, and the durability of the immunity conferred by the vaccine are all factors that contribute to these doubts [2]. By February 2021, 289 vaccines were in development, 66 were in clinical trials, out of which 20 were in phase 3. Out of the 66, 10 were authorized which were developed by the following (though for restricted use) - AstraZeneca/Oxford, BioNTech/Pfizer, Gamaleya, Moderna, Sinopharm/Beijing Institute, Bharat Biotech, and others from China, Kazakhstan and Russia. Lead producers of some vaccines had already planned collaborations with middle income countries, like AstraZeneca with India, Argentina and Thailand, and Johnson & Johnson with South Africa [6]. Several innovative technologies paved the way for the leading vaccines and further allowed them to dominate the market. Among the (eventually) leading vaccines; Oxford/AstraZeneca, Janssen and Gamaleya used adenoviral vectors, Pfizer/BioNTech and Moderna made use of mRNA platforms, Bharat BioTech and Sinopharm were inactivated viruses and Medigen and Novavax were protein subunit vaccines [7]. The vaccines were successful; today, about 72% of the global population is vaccinated [8].

While vaccinations have provided significant hope for controlling the spread of the COVID-19 virus, concerns about potential side effects persist. A comprehensive study conducted in the UAE, where the majority of recipients received either the Pfizer/BioNTech or Sinopharm vaccines, identified several common adverse effects. The most frequently reported side effect was pain, which occurred in the joints, muscles, and at the injection site. Additionally, recipients reported that they experienced headaches, fatigue, and drowsiness. These side effects were notably more prevalent among those who received the mRNA-based Pfizer/BioNTech vaccine compared to those who were administered the Sinopharm vaccine [9]. A similar study was taken in Iran with most recipients vaccinated by AstraZeneca (covishield) or Sputnik V. According to the results, 79% of recipients experienced fatigue, and over 70% experienced other symptoms like pain in the site of injection and body pain. However, these symptoms faded away in less than three days for the majority of the recipients [10]. Though a majority of side effects were mild, studies have been done revealing incidences post vaccination relating to adverse reactions in the skin, allergic responses (like anaphylaxis) and thromboembolic events [11]. One report stated that 18.8% of recipients with serious adverse effects were affected by a thromboembolic event [12]. Given recent reports linking certain COVID-19 vaccines to rare cases of thrombosis and thromboembolism, understanding and monitoring these potential complications has become all the more serious. In this context, exploring the relevance of long-term vaccine side effects, including thrombotic events, becomes imperative as societies strive for both immediate protection and long-term public health resilience against COVID-19. Hence, this article will evaluate the thrombotic related events post COVID-19 vaccination.

2. Thrombosis and its link with available COVID Vaccines

Thrombosis, which refers to the formation of blood clots within blood vessels, and thromboembolism, a condition where a clot formed in a vessel travels to another part of the body, represent critical medical concerns due to their potential severe nature. Thrombosis can manifest in various forms, which can be categorized into arterial or venous. Both thrombosis and thromboembolism can be very serious, for example, arterial clots can lead to myocardial infarctions (heart attacks) and strokes, while venous thromboembolism can lead to pulmonary embolism, a potentially fatal blockage in the lungs. Venous thromboembolism is the third most common cause of death worldwide [13]. Thrombocytopenia increases the risk of thrombosis, for example, in the case of heparin-induced thrombocytopenia. In this case, the presence of heparin may lead to the production of IgG antibodies. These antibodies attach to the platelets and activate them, causing them to release microparticles which, as released, leads to platelet consumption and hence thrombocytopenia. These microparticles promote thrombin generation, increasing risk of thrombosis [41]. Heparin-induced thrombocytopenia with thrombosis (HITT) could be split into two main causes: a hypercoagulable state or vascular damage [14].

Recent concerns have arisen regarding the potential link between certain COVID-19 vaccines and rare cases of thrombosis with thrombocytopenia syndrome (TTS). This condition involves the development of blood clots combined with low platelet counts, often occurring in unusual sites such as the brain (cerebral venous sinus thrombosis) or the abdomen. While the exact mechanism remains under investigation, it is hypothesized that it has to do with the spike proteins' interaction with receptors like C type lectin receptors and CD147, or PF4 antibodies [15]. Another theory suggests that the protein may be acting on platelets and causing damage to the endothelial wall (by downregulating ACE2) [16]. The link has been found in astrazeneca and johnson & johnson supposedly because they both possess a viral vector, whereas mrna vaccines like Pfizer and Moderna did not result in thrombotic events as they do not contain the polyanionic molecules required to develop VITT [17]. Understanding the association between COVID-19 vaccines and thrombosis with thrombocytopenia is crucial for balancing the benefits of vaccination in preventing severe illness from COVID-19 with the potential risks of rare adverse events.

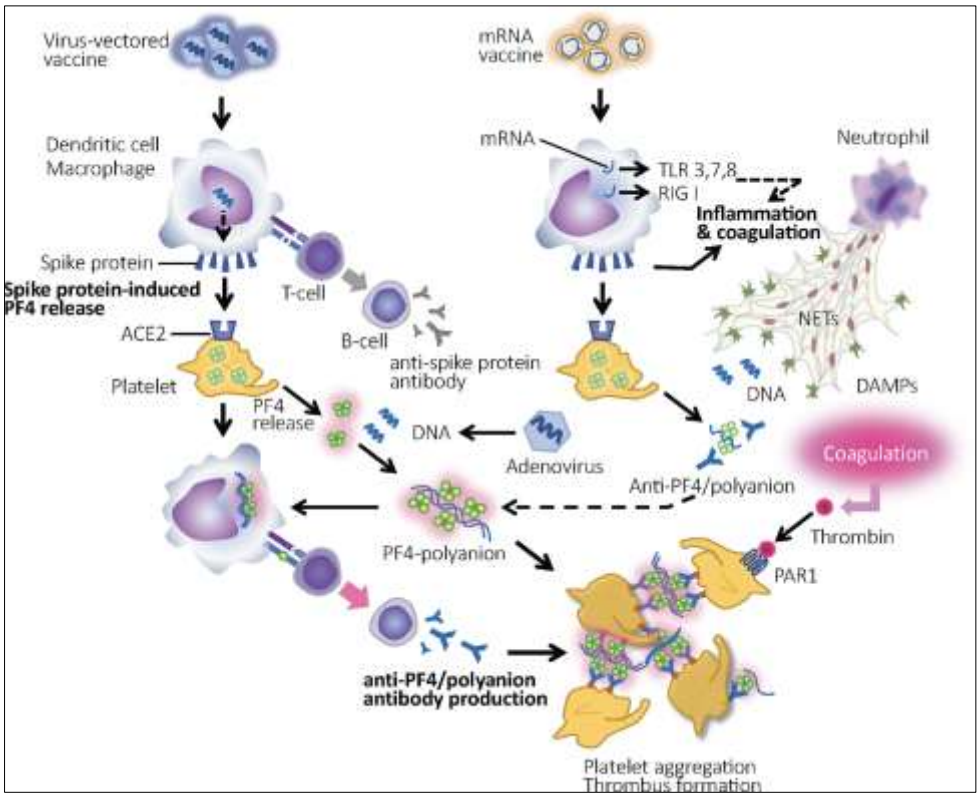

Figure 1 Potential cause of thrombosis and thrombocytopenia post vaccination [16]

2.1. Studies Showing Link between AstraZeneca vaccine and TTS

The AstraZeneca vaccine, also known as the ChAdOx1 vaccine, was first administered outside of clinical trials on January 4, 2021. Remarkably, within less than 12 months, over two billion doses of this vaccine were distributed globally. This reached more than 170 countries, with a significant focus on ensuring equitable access. Approximately two-thirds of the distributed doses were allocated to lower- and middle-income countries [18]. ChAdOx1 is an adenoviral vector vaccine with an efficacy of 72% [39]. Concerns with the vaccine arose when it was linked to rare cases of thrombosis with thrombocytopenia syndrome (TTS); a serious adverse event with a high mortality rate of about 35.9% [19].

On 10th March, the European Medicines Agency published a report recording 4 cases within Austria of thrombosis in people receiving vaccination with a single batch of the vaccine, which included one death and two serious cases. Though the batch was scrapped from use, similar events were noted with the vaccine. In the UK, by 31 March, a healthcare agency in the UK reported 79 cases of thrombosis (related to thrombocytopenia). 44 of these were cerebral venous sinus thrombosis (in the brain). Out of 79, 51 cases were women, 28 cases were men, and 19 were fatal in total. The entirety of these cases were recognized after the first dose. It was noticed that the risk of the adverse event was lower in older age groups (1.1/100000) than in younger age groups (0.2/100000). Though the risk in younger ages (20-29 years) is higher, the risk is still relatively low (a women taking contraceptives has a thrombotic risk of 60/100000) [20]. The UK report overall highlighted that although a thrombotic risk is present, the benefits outweigh the risks [21]. By May 2021, the incidence of TTS was estimated as 13.6 in one million doses after the first dose of vaccination, and 1.8 in one million after following doses [40]. This is an assuringly low risk, however may raise concerns as it has recorded a high fatality rate of 18% [17]. As for cerebral venous sinus thrombosis, the cumulative incidence (following astrazeneca vaccine) presents to be 0.32-6.5 per 100000 individuals [22].

2.2. Studies Showing Link between Johnson&Johnson vaccine and TTS

Similar to the AstraZeneca vaccine, the Johnson & Johnson vaccine employs an adenoviral vector. This approach involves modifying the DNA within an adenovirus to elicit an immune response. One notable advantage of the Johnson & Johnson vaccine is its ease of storage compared to other vaccines, as it does not require extremely low temperatures [23]. By March 2021, over 20 million doses had been shipped to the United States. Furthermore, within the first half of 2021, an impressive total of 100 million doses were delivered [24]. The Advisory Commission on Immunization Practices (ACIP) met on April 12, 2021, to discuss the grave side effects that six patients had from receiving the Johnson and Johnson (J&J) COVID-19 vaccine. The Centers for Disease Control and Prevention (CDC) and the US Food and Drug

Administration (FDA) jointly advised delaying the use of the J&J vaccination until after additional evaluation. It's interesting to note that all six of the patients included in the citations above had cerebral venous sinus thrombosis (CVST), were female Caucasian women between the ages of 18 and 40, and had thrombocytopenic results. These 6 cases (including thrombocytopenia, with platelet counts lower than 150000/mm^3) were reported when about 6.86 million doses were given. However, this comparative risk was not very high, for reference, AstraZeneca had reported 23 TTS cases within only the first week [25]. A case of deep vein thrombosis (DVT) was reported in a 44-year-old woman following administration of the Johnson & Johnson vaccine. Despite the presence of predisposing factors that could have contributed to her condition, this incident raised concerns about whether the vaccine might increase the risk of thrombotic events [26]. However, after thorough analysis, health authorities concluded that the benefits of the vaccine far outweigh the potential risks associated with such adverse events. Consequently, despite the reported case, 30 million doses were delivered to the UK [21].

2.3. Studies Showing Link between other CoVID-19 vaccines and TTS

AstraZeneca and Janssen are adenoviral vector vaccines, and it is interesting to note that Sputnik V, though vector-based, did not report any thrombotic results [27]. Sinopharm, an inactivated virus vaccine, also showed no correlation with thrombosis. A study among healthcare employees reported elevated heparin levels in 7 cases out of 406, however none of these showed signs of VITT, TTS or other thrombotic conditions [28]. This could signify that inactivated virus vaccines have a lower risk for thrombotic-related conditions than vector-based, etc., which highlights the safety of such vaccines [29]. mRNA vaccines, like Pfizer and Moderna, have also shown very minimal relation to thrombotic events. Pfizer is hard to store (low temperature conditions) but it has a very high efficacy [30]. A case of deep vein thrombosis (DVT) was reported following administration of the Pfizer vaccine, alongside a separate instance of immune thrombocytopenia characterized by symptoms such as petechiae and gum bleeding in a patient without predisposing conditions (in early 2021) [31,32]. However, it remains challenging to directly attribute these events to vaccine-induced thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS) due to the rarity of such occurrences and the possibility that they may be coincidental. The relationship between these isolated adverse events and the vaccine is not definitively established, so further investigation may be required. Regarding the Moderna vaccine, there was one reported case of thrombocytopenia in a 60-year-old man, although this incident was not categorised as vaccine-induced thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS). Additionally, an acute case of deep vein thrombosis (DVT) was observed in a 27-year-old individual. While these events may potentially be linked to anti-platelet factor 4 (PF4) antibodies, the overall risk of developing thrombosis after receiving the Moderna vaccine remains very low [33,34]. Covaxin, by Bharat Biotech, was taken as a vaccination by about 12% of India's vaccinated population. As analyzed by the AEFI (Adverse effects following immunization) committee, there are no thrombotic events reported post the covaxin vaccination [38]

Table 1 Vaccines used in this article in order of the number of thrombotic related cases reported (highest first)

Vaccine Manufacturer	Scientific name	Type of vaccine	Relative safety in terms of thrombosis
AstraZeneca/ Covishield	ChAdOx1 nCoV-19	Adenoviral vector	Highest risk of thrombotic cases (predisposing factors may be checked)
Johnson & Johnson	Ad26.COV2.S	Adenoviral vector	Second highest risk (symptoms post vaccination should be looked out for)
Pfizer-BioNTech	BNT162b2	mRNA	Negligible thrombotic risk
Moderna	CX-024414	mRNA	Negligible thrombotic risk
Sinopharm	Sinopharm BIBP COVID-19	Inactivated virus	Negligible thrombotic risk
Gamaleya	Sputnik V	Adenoviral vector	Negligible thrombotic risk
Bharat BioNTech	Covaxin BBV152	Inactivated virus	No thrombotic risk

Since VITT is relatively recent, there is still much to be learned about how VITT can be treated and prevented, however there are a couple measures that may be taken based on clinical evidence. These support the use of anticoagulants (in

particular, non-heparin anticoagulants), like fondaparinux, thrombin inhibitors like bivalirudin or oral anticoagulants [35]. Another possible treatment option is high dose IVIG, as it was previously used to treat heparin induced thrombocytopenia, before the discovery of VITT [35]. It should be a precautionary measure to identify VITT symptoms as early as possible. An evaluation should be carried out If a patient experiences symptoms like petechiae, leg pain, swelling, shortness of breath, back pain, nausea, abdominal pain, visual changes, or a severe headache. Though VITT is characterised by thrombosis as well as a low platelet count, a patient post vaccination with only thrombosis (but normal platelets) may be in an early stage of VITT, so this should be kept in mind [36]. Though the risk is very low, patients with high predisposing conditions may want to opt for an appropriate vaccine in the future. Symptoms of VITT can be spotted anywhere from 4-42 days after vaccination [37]. A flow chart describing the treatment strategies used for VITT is given as follows.

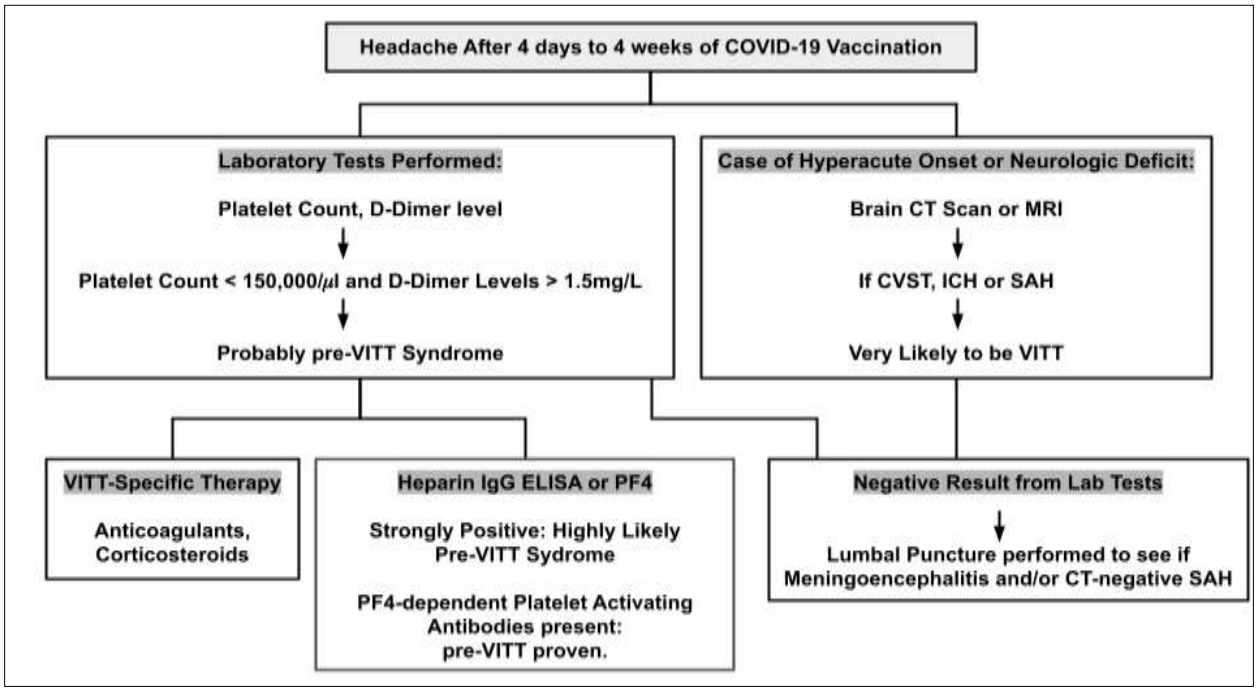

Figure 2 Treatment Strategies Adapted for VITT (CVST= Cerebral venous sinus thrombosis, ICH= Intracerebral hemorrhage, SAH= subarachnoid hemorrhage)

To enhance vaccine safety, research and surveillance should be continued, because an understanding of the mechanisms behind these events could help improve safety measures.

3. Conclusion

The production and distribution of COVID-19 vaccines has been integral in controlling the spread of SARS-CoV-2, and lowering its impact on societies. This article covers a variety of vaccines and their connection with thrombotic events. Though even the highest thrombotic risk is very low, it should not be neglected considering the fatality of the condition.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Wu, F., Zhao, S., Yu, B., Chen, Y.M., Wang, W., Song, Z.G., Hu, Y., Tao, Z.W., Tian, J.H., Pei, Y.Y. and Yuan, M.L., 2020. A new coronavirus associated with human respiratory disease in China. Nature, 579(7798), pp.265-269.

[2] Archana Koirala, Ye Jin Joo, Ameneh Khatami, Clayton Chiu, Philip N.Britton,Vaccines for COVID-19: The current state of play,Paediatric Respiratory Reviews,Volume 35,2020, Pages 43-49,ISSN 1526-0542, https://doi.org/10.1016/j.prrv.2020.06.010. https://www.sciencedirect.com/science/article/pii/S1526054220300956#b0010

[3] https://data.who.int/dashboards/covid19/cases

[4] Atyabi, S., Rommasi, F., Ramezani, M., Ghane Ezabadi, M., Arani, M., Sadeghi, M., Ahmed, M., Rajabi, A., Dehghan, N., Sohrabi, A., Seifi, M. and Nasiri, M. (2022) Relationship between blood clots and COVID-19 vaccines: A literature review. Open Life Sciences, Vol. 17 (Issue 1), pp. 401-415. https://doi.org/10.1515/biol-2022-0035

[5] Ana Macedo, Nilza Gonçalves, Cláudia Febra,COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis,Annals of Epidemiology,Volume 57,2021,Pages 14-21,ISSN 1047-2797, https://doi.org/10.1016/j.annepidem.2021.02.012. https://www.sciencedirect.com/science/article/pii/S1047279721000338#section-cited-by

[6] Wouters, O.J., Shadlen, K.C., Salcher-Konrad, M., Pollard, A.J., Larson, H.J., Teerawattananon, Y. and Jit, M., 2021. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. The Lancet, 397(10278), pp.1023-1034.

[7] Alonso Ruiz, A., Bezruki, A., Shinabargar, E. et al. Which roads lead to access? A global landscape of six COVID-19 vaccine innovation models. Global Health 20, 25 (2024). https://doi.org/10.1186/s12992-024-01017-z

[8] https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html

[9] AUTHOR=Ganesan Subhashini , Al Ketbi Latifa Mohammad Baynouna , Al Kaabi Nawal , Al Mansoori Mohammed , Al Maskari Noura Nasser , Al Shamsi Mariam Saif , Alderei Aysha Saeed , El Eissaee Hamada Nasser , Al Ketbi Rudina Mubarak , Al Shamsi Noura Saeed , Saleh Khuloud Mohammed , Al Blooshi Aysha Fahad , Cantarutti Flavia Martinez , Warren Katherine , Ahamed Faheem , Zaher Walid TITLE=Vaccine Side Effects Following COVID-19 Vaccination Among the Residents of the UAE—An Observational Study JOURNAL=Frontiers in Public Health VOLUME=10 YEAR=2022 URL=https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2022.876336 DOI=10.3389/fpubh.2022.876336

[10] Houshmand, B., Keyhan, S.O., Fallahi, H.R. et al. Vaccine-associated complications: a comparative multicenter evaluation among dental practitioners and dental students—which candidate vaccine is more safe in SARS COV II, Gam-COVID-Vac (Sputnik V), ChAdOx1 nCoV-19 (AstraZeneca), BBV152 (Covaxin), or BBIBP-CorV(Sinopharm)?. Maxillofac Plast Reconstr Surg 44, 3 (2022). https://doi.org/10.1186/s40902-021-00330-6

[11] Rabail, Roshina, Waqar Ahmed, Madiha Ilyas, Muhammad Shahid Riaz Rajoka, Abdo Hassoun, Abdur Rauf Khalid, Moazzam Rafiq Khan, and Rana Muhammad Aadil. 2022. "The Side Effects and Adverse Clinical Cases Reported after COVID-19 Immunization" Vaccines 10, no. 4: 488. https://doi.org/10.3390/vaccines10040488

[12] Aravind P. Gandhi, U. Venkatesh, Naveen Murali, Serious adverse event following immunization and thromboembolic events associated with COVID19 vaccination: An analysis of nationwide causality assessment from India, Indian Heart Journal, Volume 75, Issue 2, 2023, Pages 139-144, ISSN 0019-4832, https://doi.org/10.1016/j.ihj.2023.02.004.

[13] Pastori, Daniele, Vito Maria Cormaci, Silvia Marucci, Giovanni Franchino, Francesco Del Sole, Alessandro Capozza, Alessia Fallarino, Chiara Corso, Emanuele Valeriani, Danilo Menichelli, and et al. 2023. "A Comprehensive Review of Risk Factors for Venous Thromboembolism: From Epidemiology to Pathophysiology" International Journal of Molecular Sciences 24, no. 4: 3169. https://doi.org/10.3390/ijms24043169

[14] Walenga, J.M., Jeske, W.P. & Messmore, H.L. Mechanisms of Venous and Arterial Thrombosis in Heparin-Induced Thrombocytopenia. J Thromb Thrombolysis 10 (Suppl 1), 13–20 (2000). https://doi.org/10.1023/A:1027372901367

[15] Lundstrom, Kenneth, Debmalya Barh, Bruce D. Uhal, Kazuo Takayama, Alaa A. A. Aljabali, Tarek Mohamed Abd El-Aziz, Amos Lal, Elrashdy M. Redwan, Parise Adadi, Gaurav Chauhan, and et al. 2021. "COVID-19 Vaccines and Thrombosis—Roadblock or Dead-End Street?" Biomolecules 11, no. 7: 1020. https://doi.org/10.3390/biom11071020

[16] Toshiaki Iba, Jerrold H. Levy,Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination,Trends in Cardiovascular Medicine,Volume 32, Issue 5, 2022,Pages 249-256,ISSN 1050-1738, https://doi.org/10.1016/j.tcm.2022.02.008.

[17] Marco Marietta, Valeria Coluccio, Mario Luppi,Potential mechanisms of vaccine-induced thrombosis,European Journal of Internal Medicine,Volume 105, 2022,Pages 1-7,ISSN 0953-6205, https://doi.org/10.1016/j.ejim.2022.08.002.

[18] https://www.astrazeneca.com/media-centre/press-releases/2021/two-billion-doses-of-astrazenecas-covid-19-vaccine-supplied-to-countries-across-the-world-less-than-12-months-after-first-approval.html#

[19] Hwang J, Park SH, Lee SW, Lee SB, Lee MH, Jeong GH, Kim MS, Kim JY, Koyanagi A, Jacob L, Jung SY, Song J, Yon DK, Shin JI, Smith L. Predictors of mortality in thrombotic thrombocytopenia after adenoviral COVID-19 vaccination: the FAPIC score. Eur Heart J. 2021 Oct 14;42(39):4053-4063. doi: 10.1093/eurheartj/ehab592. PMID: 34545400; PMCID: PMC8500026.

[20] BMJ 2009; 339 doi: https://doi.org/10.1136/bmj.b2890

[21] BMJ 2021; 373 doi: https://doi.org/10.1136/bmj.n958

[22] Guetl, Katharina, Reinhard Bernd Raggam, and Thomas Gary. 2022. "Thrombotic Complications after COVID-19 Vaccination: Diagnosis and Treatment Options" Biomedicines 10, no. 6: 1246. https://doi.org/10.3390/biomedicines10061246

[23] Livingston EH, Malani PN, Creech CB. The Johnson & Johnson Vaccine for COVID-19. JAMA. 2021;325(15):1575. doi:10.1001/jama.2021.2927

[24] https://www.jnj.com/media-center/press-releases/johnson-johnson-covid-19-vaccine-authorized-by-u-s-fda-for-emergency-usefirst-single-shot-vaccine-in-fight-against-global-pandemic

[25] Malik B, Kalantary A, Rikabi K, et alPulmonary embolism, transient ischaemic attack and thrombocytopenia after the Johnson & Johnson COVID-19 vaccineBMJ Case Reports CP 2021;14:e243975. https://doi.org/10.1136/bcr-2021-243975

[26] Ayrton Bangolo, Jeffin Cherian, Mohamed Ahmed, Ali Atoot, Bhavna Gupta, Adam Atoot, "A Case Report of DVT following the Johnson and Johnson Vaccine against the Novel SARS-CoV-2", Case Reports in Infectious Diseases, vol. 2022, Article ID 1292754, 3 pages, 2022. https://doi.org/10.1155/2022/1292754

[27] Nogrady B. Mounting evidence suggests Sputnik COVID vaccine is safe and effective. Nature. 2021;595(7867):339–40.10.1038/d41586-021-01813-2

[28] Tingting Liu, Jing Dai, Zhitao Yang, Xiaoqi Yu, Yanping Xu, Xinming Shi, Dong Wei, Zihan Tang, Guanqun Xu, Wenxin Xu, Yu Liu, Ce Shi, Qi Ni, Chengde Yang, Xinxin Zhang, Xuefeng Wang, Erzhen Chen, Jieming Qu, Inactivated SARS-CoV-2 vaccine does not influence the profile of prothrombotic antibody nor increase the risk of thrombosis in a prospective Chinese cohort, Science Bulletin, Volume 66, Issue 22, 2021, Pages 2312-2319, ISSN 2095-9273,https://doi.org/10.1016/j.scib.2021.07.033

[29] Atyabi, S., Rommasi, F., Ramezani, M., Ghane Ezabadi, M., Arani, M., Sadeghi, M., Ahmed, M., Rajabi, A., Dehghan, N., Sohrabi, A., Seifi, M. and Nasiri, M. (2022) Relationship between blood clots and COVID-19 vaccines: A literature review. Open Life Sciences, Vol. 17 (Issue 1), pp. 401-415. https://doi.org/10.1515/biol-2022-0035

[30] Doroftei, Bogdan, Alin Ciobica, Ovidiu-Dumitru Ilie, Radu Maftei, and Ciprian Ilea. 2021. "Mini-Review Discussing the Reliability and Efficiency of COVID-19 Vaccines" Diagnostics 11, no. 4: 579. https://doi.org/10.3390/diagnostics11040579

[31] Carli, G., Nichele, I., Ruggeri, M. et al. Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. Intern Emerg Med 16, 803–804 (2021). https://doi.org/10.1007/s11739-021-02685-0

[32] https://doi.org/10.1002/ajh.26106

[33] https://atm.amegroups.org/article/view/77765/html

[34] Malayala S V, Mohan G, Vasireddy D, et al. (March 25, 2021) Purpuric Rash and Thrombocytopenia After the mRNA-1273 (Moderna) COVID-19 Vaccine. Cureus 13(3): e14099. doi:10.7759/cureus.14099

[35] Gabarin N, Arnold DM, Nazy I, Warkentin TE. Treatment of vaccine-induced immune thrombotic thrombocytopenia (VITT). Semin Hematol. 2022;59(2):89-96. doi:10.1053/j.seminhematol.2022.03.002

[36] https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

[37] Salih F, Kohler S, Schönborn L, Thiele T, Greinacher A, Endres M. Early recognition and treatment of pre-VITT syndrome after adenoviral vector-based SARS-CoV-2 vaccination may prevent from thrombotic complications:

review of published cases and clinical pathway. Eur Heart J Open. 2022;2(3):oeac036. Published 2022 May 16. doi:10.1093/ehjopen/oeac036

[38] https://www.newindianexpress.com/nation/2021/May/17/minuscule-risk-of-blood-clots-with-covishield-no-clots-yet-with-covaxin-expert-panel-2303681.html

[39] https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/astrazeneca-admits-its-covid-vaccine-can-cause-rare-side-effect/articleshow/109710995.cms

[40] Chandini Raina MacIntyre, Benjamin Veness, David Berger, Nada Hamad, Noor Bari,Thrombosis with Thrombocytopenia Syndrome (TTS) following AstraZeneca ChAdOx1 nCoV-19 (AZD1222) COVID-19 vaccination – A risk–benefit analysis for people < 60 years in Australia,Vaccine,Volume 39, Issue 34,2021,Pages 4784-4787,ISSN 0264-410X, https://doi.org/10.1016/j.vaccine.2021.07.013.

[41] Ahmed, I., Majeed, A., & Powell, R. (2007). Heparin induced thrombocytopenia: diagnosis and management update. Postgraduate medical journal, 83(983), 575–582. https://doi.org/10.1136/pgmj.2007.059188