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Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierv20

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To cite this article: Abdolreza Esmaeilzadeh, Armin Jahani Maleki, Amirhosein Moradi, Amir Siahmansouri, Mohammad Javad Yavari, Parsa Karami & Reza Elahi (2022) Major severe acute respiratory coronavirus-2 (SARS-CoV-2) vaccine-associated adverse effects; benefits outweigh the risks, Expert Review of Vaccines, 21:10, 1377-1394, DOI: 10.1080/14760584.2022.2116008

To link to this article: https://doi.org/10.1080/14760584.2022.2116008

Published online: 24 Aug 2022.

EXPERT REVIEW OF VACCINES
2022, VOL. 21, NO. 10, 1377–1394
https://doi.org/10.1080/14760584.2022.2116008

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REVIEW

Major severe acute respiratory coronavirus-2 (SARS-CoV-2) vaccine-associated adverse effects; benefits outweigh the risks

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ABSTRACT

Introduction: Since its emergence, there have been huge efforts to design vaccines against coronavirus disease 2019 (COVID-19) to inhibit its interpersonal spread. Global vaccine development is the most promising cost-effective method for overcoming the epidemic. However, following reports of post-vaccination thromboembolic adverse effects, there have been raising concerns about the safety profile of the COVID-19 vaccine.

Areas covered: We aimed to review the recent Food and Drug Administration (FDA)-approved vaccines and identify the organ-based major complications of COVID-19 vaccines based on reliable published studies. To find high-quality and large-scale observational, clinical trial, and cohort studies, PubMED, Scholar, Embase, and Web of Science were searched using keywords: COVID-19, SARS-CoV-2, vaccine, Pfizer (BNT162b2), Johnson and Johnson (Ad26.COV2), Moderna (mRNA-1273), Oxford AstraZeneca (ChAdOx1nCoV19), Coronavac (Sinovac), BBIBP-CorV (Sinopharm), adverse effect, and complication. To include all relevant articles, backward searching was also done on similar article citations. Case reports, studies including less than 10 participants, and biased articles were excluded.

Expert opinion: Based on data from high-quality and population-based studies, major adverse effects are divided into four major organ-specific groups, including cardiovascular, neurologic, hematologic, and immune-allergic side effects. The incidence of most of these side effects is not different between vaccinated and normal populations, and currently, the benefits of vaccination against COVID-19 are greater than the mortality and morbidity risks of COVID-19 infection. However, further studies, specifically systematic review and meta-analysis, are still indicated to investigate further unknown side effects of these vaccines and the existence of causality between the vaccine and reported adverse events.

ARTICLE HISTORY
Received 28 April 2022
Accepted 18 August 2022

KEYWORDS
Vaccine; coronavirus-disease 2019 (COVID-19); severe acute respiratory coronavirus 2 (SARS-CoV-2); adverse effect

1. Introduction

Since late 2019, the coronavirus disease 2019 (COVID-19) pandemic has caused enormous health and economic issues in almost all countries [1,2]. The virus causing the disease is named severe acute respiratory syndrome coronavirus 2019 (SARS-CoV-2) [3–6]. Since the beginning of the pandemic, there has been a huge effort to block the infection and interpersonal transmission of COVID-19. Based on data from the World Health Organization (WHO), as of 12 March 2022, more than 460 million confirmed cases with more than 6 million deaths have been reported (WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data, accessed on 17 March 2022). Despite the efforts, no drugs have been approved for treatment by the Food and Drug Administration (FDA), yet. Therefore, the development of the vaccine is the most hopeful approach to blocking the spread of the disease. By the middle of March 2022, more than 11 billion doses of vaccine have been injected into more than 63% of the global population who have received at least one dose (https://ourworldindata.org/covid-vaccinations?country=OWID_WRL, accessed on 17 March 2022).

To find high-quality and large-scale observational, clinical trial, and cohort studies, PubMED, Scholar, Embase, and Web of Science were searched using keywords: COVID-19, SARS-CoV-2, vaccine, Pfizer (BNT162b2), Johnson and Johnson (Ad26.COV2), Moderna (mRNA-1273), Sinopharm (ChAdOx1), Coronavac (Sinovac), BBIBP-CorV (Sinopharm), adverse effect, and complication. To include all relevant articles, backward searching was also done on similar article citations. Case reports, studies including less than 10 participants, and biased articles were excluded.

Despite the necessity and benefits of vaccination, there have been raising concerns about the safety and adverse effects of the vaccine, specifically after reports of thromboembolic events [7]. Therefore, under-vaccinated or unvaccinated communities could contribute to the intuition and spread of outbreaks. Considering the empowerment of the anti-vaccine movement with the internet, more people might be struggling

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Article highlights

- Currently, Pfizer (BNT162b2), Johnson and Johnson (Ad26.COV2), Moderna (mRNA-1273), Oxford AstraZeneca (ChAdOx1nCoV19), Coronavac (Sinovac), and BBIBP-CorV (Sinopharm) are the FDA-approved vaccines for COVID-19.
- Hematologic, neurologic, cardiovascular, and immune-allergic adverse effects are the four main categories of COVID-19 vaccine-associated major side effects.
- Among hematologic side effects, vaccine-induced thrombotic thrombocytopenia (VITT) and disseminated intravascular coagulation (DIC) are the main adverse effects with the highest incidence after COVID-19 vaccines.
- To the best of our knowledge, the incidence of other side effects in vaccinated individuals is not higher than COVID-19 infected population.
- Overall, the benefits of vaccination against COVID-19 outweigh the risks associated with vaccination against COVID-19.

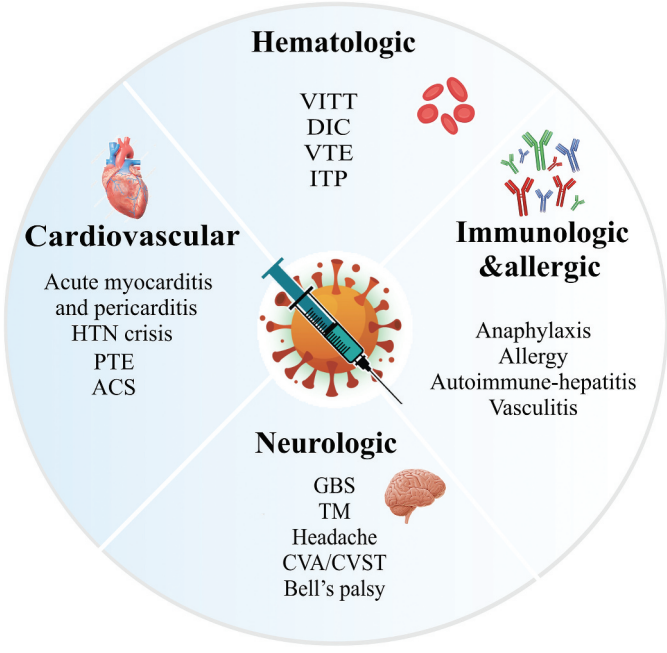

Figure 1. Major system-based adverse events of COVID-19 vaccination. VITT: vaccine-induced thrombotic thrombocytopenia, DIC: diffuse intravascular coagulation, VTE: venous thromboembolism, ITP: immune thrombocytopenia, HTN: hypertension, PTE: pulmonary thromboembolism, ACS: acute coronary syndrome, GBS: Guillain–Barré syndrome. TM: transverse myelitis, CVA: cerebrovascular attack, CVST: cerebral venous sinus thrombosis. Created by Elahi et al.

with vaccine hesitancy, also known as anti-vaccine sentiment [8,9]. Clear, comprehensive, and authentic studies addressing the real-world experience of the safety profile of vaccines could serve as a potent strategy against anti-vaccine movements. Therefore, this article aims to review COVID-19-vaccine-associated organ-specific adverse effects (Figure 1) based on high-quality data from population-based studies, cohorts, and clinical trials.

2. Development of vaccines against SARS-CoV-2

Different vaccines with distinct platforms have been developed. Some of these vaccines have been FDA-approved and are being administered worldwide [10]. These vaccines are of different classes and are produced by different methods and technologies. mRNA vaccines, including mRNA-1273 (Moderna), and BNT162b2 (Pfizer/BioNTech), were among the first approved vaccines and have been widely used in several European countries and the United States. Adenoviral vectors, including ChAdOx1nCoV19 (Oxford AstraZeneca) and Ad26.COV2.S (Johnson & Johnson) are the other developed vaccines that are designed to express the viral target spike through the expression of its genome by the adenoviral DNA structure. Inactivated viruses, including Coronavac (Sinovac) and BBIBP-CorV (Sinopharm), and whole-genome vaccines including COVAXIN (Bharat Biotech) are other vaccines approved by the WHO. Moreover, several other vaccines of different platforms are under investigation in different countries (https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_02March2022.pdf). Moreover, vaccines are named differently in different countries. Examples are Comirnaty (developed by BioNTech and Pfizer), Jcovden (previously COVID-19 Vaccine Janssen), Nuvaxovid (a recombinant spike (S) protein nanoparticle vaccine), Spikevax (previously COVID-19 Vaccine Moderna), and Vaxzevria (previously COVID-19 Vaccine AstraZeneca). In this article, adverse effects associated with these FDA-approved vaccines have been reviewed. The European agency responsible for the authorization of SARS-CoV-2 vaccines is the European Medicine Agency (EMA).

3. Hematologic side effects

Several articles have been reporting thrombosis following SARS-CoV-2 vaccine administration. The exact underlying mechanisms for these thrombotic events are not clearly determined. Hypothetically, several factors, such as increased activated platelets and dysregulated complement activation, are thought to be involved [11]. Notably, the risk of thrombotic events related to adenovirus-based vaccines, such as AstraZeneca, is higher than mRNA vaccines that have caused the restriction of AstraZeneca's application in several countries [12]. The reason could be the cross-reactivity between the adenoviral vector and platelet factor that could result in an autoimmune response. Moreover, increased entry of adenoviral vector to the platelet could result in higher expression of surface spike protein on platelets. Lastly, the wild type of spike proteins compared to the recombinant type that exists in mRNA vaccines could result in a higher risk of thrombosis following adenovirus-based vaccines [13]. Most reports of hematologic side effects include thrombotic events that are described below.

3.1. *Vaccine-induced thrombotic thrombocytopenia (VITT)*

The co-occurrence of thrombocytopenia and thrombosis is called Thrombotic Thrombocytopenia (TTP). However, when this syndrome happens after receiving the vaccine, it is called 'vaccine-induced thrombotic thrombocytopenia (VITT)' [14,15]. The majority of VITT cases have been reported after the administration of AstraZeneca (Table 1). However, it has also been reported after Johnson and Johnson [16]. Thrombosis in

Table 1. Selected high-quality cross-sectional, cohort, and systematic review studies of post-COVID-19 vaccine adverse effects. Created by Elahi et al.

Author	Study design and size	Vaccine(s)	Country	Results	Ref.
Perry et al.	A total of 95 patients data was gathered from 43 hospitals across the UK which 70 patients had VITT and 25 patients did not.	ChAdOx1	UK	Increased risk of VITT/CVT after the first dose of ChAdOx1.	[42]
Andrews et al.	Venous thrombosis and thrombocytopenia cases were reported to the national Covid-19 immunization register between 30 November 2020 and 18 April 2021.	ChAdOx1 BNT162b2	UK	Increased risk of VITT/CVT after ChAdOx1 first dose in individuals <65 within a month.	[135]
Kewan et al.	A total of 1842 patients were referred to the emergency department (ED) within 10 days of vaccination. 1221 patients were referred to ED after the first dose of the vaccine and 623 after the second dose.	BNT-162b2 mRNA-1273 Ad26.COV2.S	USA	ED admissions were not statistically different between vaccinated and not vaccinated groups.	[23]
Laporte et al.	The authors examined three groups including 1,662,719 people 10 years of age and over with the first dose of vaccine, 622,778 people with the second dose of vaccine, and 190,616 people who were diagnosed with COVID-19 between 1 January 2021 and 18 April 2021. Also, they compared the clinical presentation rate of VTE with the reference population (7,013,040 people referred to the health care system in 2019).	Moderna ChAdOx1 Pfizer	Spain	Increased risk of VTE with or without thrombocytopenia in usual or unusual anatomic regions.	[24]
Schulz et al.	A total of 45 CVT cases after the first dose of ChAdOx1 within 1 month were included.	BNT162b2 ChAdOx1 mRNA-1273	Germany	Increased risk of CVT, especially in women, within one month after ChAdOx1.	[126]
Hippisley-Cox et al.	19,608,088 people who received the first dose of ChAdOx1, 9,513,625 received the first dose of BNT162b2, and 1,758.095 people with positive SARS-CoV-2 test were included.	BNT162b2 ChAdOx1	UK	Higher risk of VTE, arterial thrombosis, and thrombocytopenia after ChAdOx1 first dose. Increased risk of ischemic stroke and arterial thromboembolism after BNT162b2 first dose. The incidence of these events in these populations was much lower than COVID-19 infection in the population.	[57]
Hwang et al.	A total of 40 patients with CVT were included in the study. 28 patients received ChAdOx1 and 12 patients received Ad26.COV.2.S.	Ad26.COV.2.S ChAdOx1	USA	CVT with Johnson and Johnson presents later than CVT after Oxford AstraZeneca.	[25]
Kerr et al.	Self-controlled case series study among 11,637,157 individuals who were vaccinated with ChAdOx1 and BNT162b2.	ChAdOx1 BNT162b2	UK Scotland Wales	Small increased risk of CVST after ChAdOx1 first dose, but not BNT162b2.	[26]
Sørvoll et al.	492 health care workers who were vaccinated with the first dose of ChAdOx1 were included in the study.	ChAdOx1	Norway	Low prevalence of thrombocytopenia and anti-PF4 antibodies (VITT) after ChAdOx1 in healthcare workers.	[21]
Riad et al.	The cross-sectional survey-based study was performed between 27 January 2021 to 27 February 2021. A total of 877 individuals were selected from 922 participants.	BNT162b2	Czech	Headache, muscle pain, fatigue, pain at the injection site, and chills were the most common post-vaccine adverse effects.	[27]
Whiteley et al.	A population-based cohort study of 46 million individuals in the UK between 8 December 2020 to 18 March 2021.	ChAdOx1 BNT162b2	UK	Elevated thrombocytopenia and intracranial venous thrombosis (ICVT) under the 70s after ChAdOx1. No relationship between arterial/venous thrombotic events and vaccination in individuals >70.	[59]
Grimshaw et al.	A prospective observational study of 704,003 people who were vaccinated with the first dose of BNT162b2.	BNT162b2	Mexico	3 GBS, 2 TM, 7 seizures, 4 weakness, and 1 radiculopathy exacerbation observed.	[98]
Mevorach et al.	304 patients with myocarditis after vaccination with BNT162b2 were analyzed.	BNT162b2	Israel	The risk of myocarditis was elevated after the BNT162b2 vaccine after the second dose between young men, but the incidence rate was still low.	[192]
Simpson et al.	2.53 million individuals who got ChAdOx1 and BNT162b2 vaccines were analyzed for the risk of ITP, thromboembolic, and hemorrhagic events.	ChAdOx1 BNT162b2	Scotland	Small elevated risk of ITP, arterial thromboembolic, and hemorrhagic adverse events after ChAdOx1. No evidence of increased risk of arterial or venous thrombotic events after BNT162b2.	[28]
Meylan et al.	A case series of individuals followed due to their suspected symptoms of adverse effects by their vital signs among the 13,296 doses of the mRNA vaccines.	BNT162b2 mRNA-1273	Switzerland	9 cases of stage III hypertension were reported.	[96]
Jabagi et al.	A population-based study evaluated the risk of cardiovascular events after SARS-CoV-2 vaccination in a specific timeline among the 3.9 and 3.2 million individuals who were 75 years old or elder that receive the first, and the second dose respectively.	BNT162b2	France	There was no increased risk of cardiovascular events after BNT162b2.	[29]
Alhazmi et al.	Retrospective, a cross-sectional study that evaluated the short-term post-vaccination side effects among the 515 participants through an online survey performed for 3 weeks	ChAdOx1 BNT162b2	Saudi Arabia	Pain at the injection site (85%), fatigue (90%), fever (66%), chills (36%), and headache (62%) were the most common side effects after ChAdOx1 and BNT162b2.	[30]
Pottegård et al.	Population-based cohort study evaluated the rates of cardiovascular and hemostatic events in the 28 days in the 281264 individuals following vaccination.	ChAdOx1	Denmark Norway	Vaccination with ChAdOx1 had an increased risk of VTE and CVT for 28 days.	[58]

(*Continued*)

Table 1. (Continued).

Author	Study design and size	Vaccine(s)	Country	Results	Ref.
Greinacher et al.	Case series of 11 patients who developed thrombosis or thrombocytopenia after SARS-CoV-2 vaccination.	ChAdOx1	Germany Austria	The risk of ITP was rarely increased after the ChAdOx1 vaccine.	[92]
Polack et al.	A randomized placebo-controlled, observer-blinded trial that investigate the safety of the BNT162b vaccine among the 43448 participants. They were divided into the 21,720 vaccine and 21,728 placebo groups.	BNT162b2	USA	Vaccination with BNT162b2 was safe and no severe adverse events were observed at least 7 days after the second dose.	[31]
Schultz et al.	Case reports of 5 patients with VTE and thrombocytopenia after SARS-CoV-2 vaccination.	ChAdOx1	Norway	Five cases of VTE and thrombocytopenia were reported 7–10 days after receiving the first dose of the ChAdOx1.	[32]
Sharifian et al. (Systematic review)	A systematic review analyzing the clinical features of the 36, and 13 patients who developed CVST and VITT 4–19 days after the first dose of the ChAdOx1 and Ad26.COV2 vaccines respectively.	ChAdOx1 Ad26.COV2	___	49 patients had post-vaccine VITT and CVST of which 19 died.	[136]
Pawlowski et al.	A retrospective cohort study analyzed the incidence rate of the CVST following vaccination in 132916 doses of SARS-CoV-2 vaccines and 771805 of the non-COVID-19 vaccines.	BNT162b2 Ad26.COV2 mRNA-1273	USA	Vaccination was not remarkably associated with CVST.	[138]
Jaiswal et al. (Systematic review)	A systematic review analyzed the baseline features, clinical presentation, treatment, and outcomes of the 80 patients who developed CVST following COVID-19 vaccination.	BNT162b2 Ad26.COV2 mRNA-1273 ChAdOx1	___	80 patients were identified to develop CVST after the vaccine from 25 studies, of whom 31 died. No difference between the vaccine type and the CVST incidence was observed.	[33]
Elberry et al. (Systematic review)	A systematic review was conducted to evaluate the demographic outcomes, commonalities, and prognosis of 173 reported VITT cases after the COVID-19 adenoviral vector-based vaccines.	Ad26.COV2 ChAdOx1	___	VITT is more common in females and young individuals. VITT commonly presents as CVT, DVT, and PTE.	[34]
Beatty et al. (Systematic review)	An online cohort study analyzed the adverse effects of the COVID-19 vaccines among the 19586 participants who were 18 years old and older.	BNT162b2 mRNA-1273 JNJ-78436735	USA	The incidence of anaphylaxis was 0.2% in fully vaccinated and 0.3% in partially vaccinated.	[162]
Lacy et al.	A total of 40 patients with previous confirmed or probable VITT after receiving the ChAdOx1 vaccine are included in this study design and 5 of the patients with ChAdOx1 Ad26.COV2, 2 of them mRNA-1273, 33 of them BNT162b2 had received as the second dose, respectively.	BNT162b2 mRNA-1273 ChAdOx1	UK	None of the patients showed any adverse effects after receiving the second dose of the vaccine.	[20]

ChAdOx1: Oxford AstraZeneca, mRNA-1273: Moderna, BNT162b2: Pfizer BioNTech, UK: United Kingdom, USA: United States of America, VITT: vaccine-induced thrombotic thrombocytopenia, CVT: cerebral vein thrombosis, VTE: venous thromboembolism, ICVT: intracranial venous thrombosis, ITP: immune thrombotic purpura, GBS: Guillain–Barré syndrome, TM: transverse myelitis, DVT: deep vein thrombosis, PTE: pulmonary thromboembolism, CVST: cerebral venous sinus thrombosis.

an unusual site with thrombocytopenia after AstraZeneca is highly suggestive of VITT. The lab data could show a positive PF4-heparin ELISA test, elevated D-dimer, and thrombocytopenia [17–20]. It has been proposed that identical to heparin-induced thrombocytopenia (HIT), the underlying mechanism for VITT could be the production of antibodies against platelet factor-4. However, all the individuals who were anti-PF4 positive did not progress to VITT after vaccination [21]. Moreover, some individuals who progressed to VITT after vaccination were anti-PF4 negative [22]. Therefore, identification of the mechanism underlying VITT needs to be established in further studies. The mechanisms of post-vaccine thrombosis formation are discussed in Figure 2.

Studies have revealed VITT after both adenoviral vector vaccines (AstraZeneca, Johnson & Johnson) [37,38] and mRNA-based vaccines (Pfizer, Moderna). However, VITT mostly happened after adenoviral vector vaccines and is less likely to happen in mRNA-based vaccines [39,40]. The incidence of VITT associated with AstraZeneca vaccine administration was reported to be about 1 case per 125,000 [41]. In a study by Perry et al., among 90 patients enrolled, 70 had experienced cerebral venous thrombosis (CVT) and the diagnosis of VITT was then given. Interestingly, all CVT cases were individuals after the administration of AstraZeneca's first dose [42]. Ankerlund et al. reported a case of VITT occurring 7 days after vaccination with the AstraZeneca vaccine. The patient was referred for persistent abdominal pain and had a history of hypertension and Hashimoto thyroiditis. The primary evaluation revealed an adrenal hemorrhage. The next day, she experienced left-sided weakness. The imaging procedure showed a huge right-sided ischemic stroke. Lab data showed positive anti-PF4 test, elevated D-dimer, and severe thrombocytopenia. Unfortunately, patients passed out 6 days after hospitalization. Due to the poor prognosis of the VITT, the authors proposed that it must be considered a principle differential diagnosis for the patient who has unusual thrombosis and thrombocytopenia, especially after vaccination [43]. Complementary data of studies addressing VITT after COVID-19 vaccines are presented in Table 1. The clinical investigation, diagnosis, and management of VITT after COVID-19 vaccine administration is out of the scope of this article and can be addressed through the guidelines defined by ISTH SSC Subcommittee on platelets immunology [44,45].

3.2. Disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC) is a type of coagulopathy that causes abnormal clot-forming or bleeding through the blood vessels. The most common promoting condition for DIC is sepsis [46]. Elevated levels of cytokines in sepsis induce the plasminogen activator inhibitor-I that finally results in clot forming and organ failure [47,48]. The timely recognition and management of DIC could prevent life-threatening consequences.

There are some reports of DIC in individuals receiving the adenoviral vector type of COVID-19 vaccine. Casucci et al. reported a case of a 52-year-old female who developed DIC about 17 days after the administration of the first dose of the Oxford-AstraZeneca vaccine. During the few hours following vaccination, she developed headache, photophobia, fever (39°), chills, nausea, and musculoskeletal pain, which were treated with paracetamol, ibuprofen, and ketorolac. After 48 hours, she returned with a relapse of fever, severe headache, and a huge ecchymosis on the left buttock. Laboratory findings demonstrated reduced platelet and fibrinogen and increased prothrombin time and D-dimer. Lower limb and abdominal ultrasonography, and intracranial and extracranial vessels MRI angiography were clear. Based on the scoring system of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Hemostasis (ISTH) (12/DIC1), she was diagnosed with overt DIC and was successfully treated with 55 mg enoxaparin and 8 mg dexamethasone for 6 days [49]. Moreover, Agostino et al. and Aladdin et al. have reported cases of cerebral venous sinus thrombosis (CVST) and multiple thrombotic organ involvement as a result of DIC that could have been related to the Oxford-AstraZeneca vaccine [50,51].

3.3. Venous and arterial thromboembolism

Venous thromboembolism (VTE) includes thrombosis in both superficial and deep veins. Studies have reported several cases of post-vaccination VTE with the Pfizer and AstraZeneca vaccines [52–56]. In a large-scale case series study by Hippisley et al., it was demonstrated that the first dose of the Pfizer vaccine was accompanied by an increased ischemic stroke and arterial thromboembolism. Moreover, Oxford-AstraZeneca was accompanied by arterial thrombosis, VTE, and thrombocytopenia. The risk of CVST was increased after both vaccines [57]. Similar results were shown in another cohort study [58]. A population-based cohort study evaluated arterial, venous, and thrombocytopenic events in 46 million individuals, of which 21 million were vaccinated with Pfizer and AstraZeneca. The results indicated that in individuals younger than 70 years old, the risk of intracranial venous thrombosis increased up to twofolds after the AstraZeneca vaccine, but not Pfizer. However, in adults over 70, vaccination was not accompanied by an increased risk of major vascular events. The authors concluded that in both ranges of age, the vaccination effect on decreasing mortality and morbidity outweighs the vascular side effects [59].

Another article by Carli et al. reported a case of a 66-year-old female with acute right-calf pain 2 days after injection of the BNT162b2 second dose. Laboratory findings including complete blood count (CBC), PTT, INR, and fibrinogen were normal. Color Doppler ultrasound was suggestive of DVT of the right peroneal vein. The patient had no history of thrombotic events, and genetic screening for coagulation factor was positive for only factor V mutation. Apixaban 10 mg/bid started for patients followed by 5 mg/bid [60]. Nevertheless, the positive factor V mutation of the patient raises questions about the causality between the vaccine and the VTE. The incidence of VTE seems to be more probable in patients with preexisting hypercoagulability.

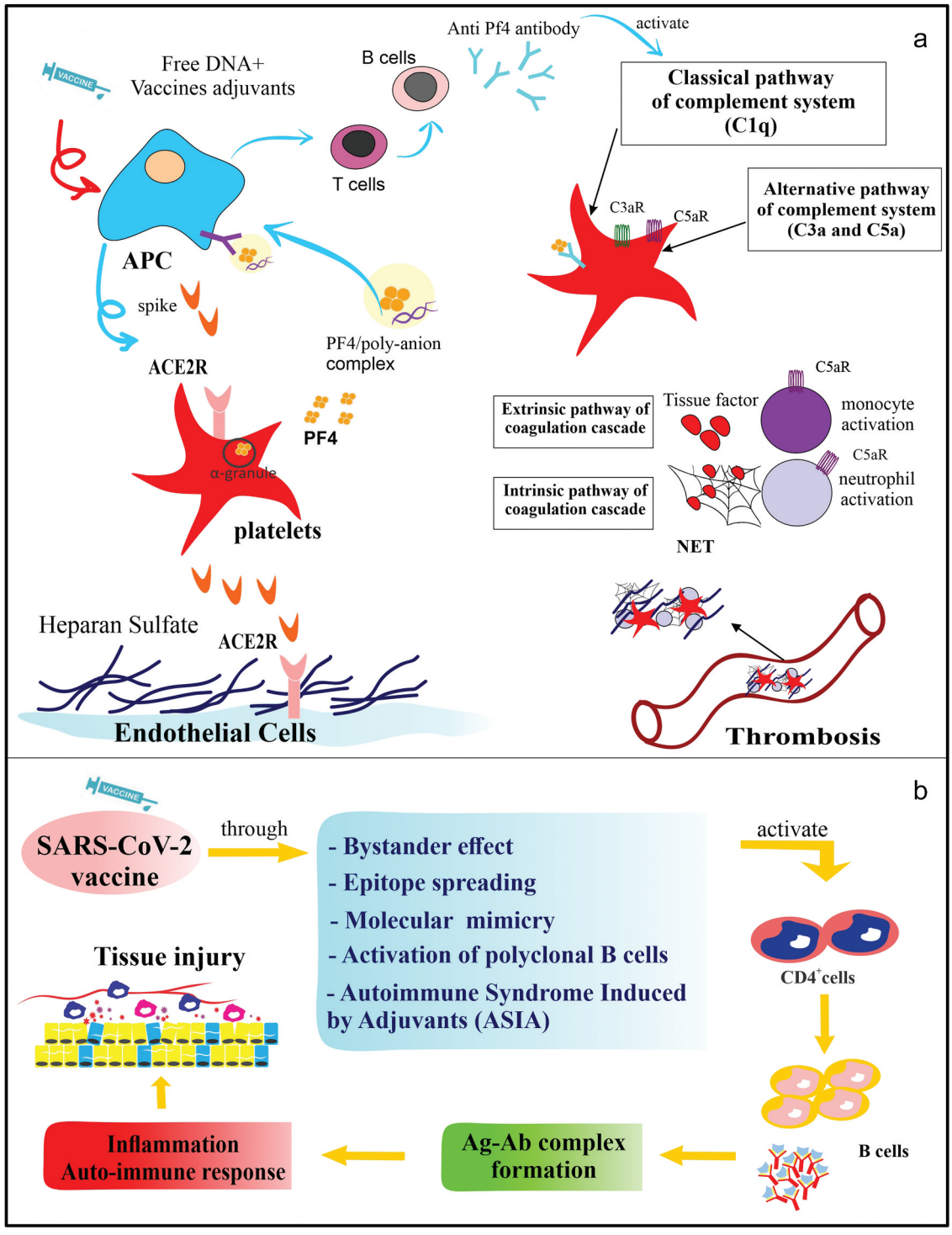

Figure 2. A: Mechanisms of post-COVID-19 vaccine thrombosis. SARS-CoV-2 spike protein after vaccination either with mRNA and adenovirus base vaccines binds to ACE2 receptor of such as (free DNA and vaccine adjuvant) convert to PF4-poly anion complex. APC presented PF4-poly anion complex to B cells then B cells secrete anti-PF4 antibodies. Anti-PF4 antibodies directly cause platelet activation and also activate both classical and alternative complement systems. Alternative complement system activation cause monocytes and neutrophils activation. Monocytes and neutrophils activate extrinsic and intrinsic coagulation pathways through tissue factor and neutrophil extracellular trap formation respectively. Altogether, platelet activation, activation of coagulation pathways, and NET formation result in bloodstream stasis and thrombosis formation [35]. B: Mechanisms of post-COVID-19 vaccine auto-immunity. The bystander effect, epitope spreading, molecular mimicry, activation of polyclonal B cells, and autoimmune syndrome induced by adjuvants (Asia) are the proposed mechanisms by which SARS-CoV-2 vaccines may activate CD4+ lymphocytes and induce an auto-antibody response. Autoantibodies produced by B cells form antigen-antibody (Ag-Ab) complexes that contribute to autoimmune inflammatory responses responsible for tissue injury [36]. Created by Elahi et al.

3.4. Immune (idiopathic) thrombocytopenia (ITP)

Immune (idiopathic) thrombocytopenia (ITP) is a condition in which immune cells produce autoantibodies against platelets and destruct them. ITP is presented by a decrease in platelet levels in the absence of a low WBC level or anemia. ITP increases the risk of bleeding in different sites and can cause bruising, petechial purpura, and even life-threatening intracranial hemorrhage [61]. Case reports have shown that ITP could happen in both adenoviral-vector-based vaccines (Johnson and Johnson and AstraZeneca) [62,63] and mRNA-based vaccines (Moderna and Pfizer) [61,64]. Based on reports from Vaccine Adverse Event Reporting System (VAERS), the incidence of thrombocytopenia after mRNA vaccines is 0.8 - per million doses [65].

In a study done by Finn et al., they reported four cases of patients with different chief complaints of petechiae, epistaxis, subconjunctival hemorrhage, and headache that were related to bleeding disorders. The patients were referred to the clinic 2–15 days after the first dose of the AstraZeneca. Their lab data revealed severe thrombocytopenia, elevated D-dimer, and negative anti-PF4. Due to the absence of thrombosis and negative anti-PF4 and ruling out other etiologies responsible for thrombocytopenia, the authors diagnosed the patients with post-vaccine ITP. The patients were treated with IVIG and glucocorticoids and only one patient needed treatment with a thrombopoietin receptor agonist (eltrombopag). All patients were finally discharged with elevated platelet levels [66].

Another matter of concern is the recurrence of ITP in the next shots. Consistently, Srikrishna et al. reported a case of a 75-year-old female who was referred to their clinic with petechiae and thrombocytopenia and elevated D-dimer found on lab data, 4 days after the booster doses of the Pfizer vaccine. This shows the importance of ITP in booster doses that requires immediate diagnosis and management [67]. The management of the ITP is done using corticosteroids, IVIG, and platelet transfusion. In severe cases that do not respond to routine management, studies have shown the benefits of the TPO agents or Rituximab. Splenectomy could also be proposed for refractory ITP [66].

Moreover, rarely, cases of autoimmune hemolytic anemia (AIHA) have been reported after vaccines of different classes; most of the cases are more associated with mRNA-based vaccines [68–70]. However, it has not yet been validated with large-scale trials or cohort studies.

4. Cardiovascular side effects

Cardiovascular complications of COVID-19 vaccination are one of the most probable side effects among others. Several studies have shown different post-vaccination cardiovascular complications, varying from benign to severe, after injection of Moderna, Pfizer-BioNTech, AstraZeneca, Jannsen, and BBIBP-CorV (Sinopharm) vaccines [71,72]. The most probable adverse effects reported by strong and large-scale studies include acute myocarditis, acute coronary syndrome, pericarditis, and hypertension crisis. However, sporadic cases of Takotsubo syndrome have been reported [73]. Most of these unwanted effects are temporary conditions with excellent outcomes, but the long-term prognosis is not yet clear.

4.1. Acute myocarditis and pericarditis

Acute myocarditis is the inflammation of the myocardium that can occur due to infection, immune system reaction, and drug-induced conditions [74,75]. Viral infections like COVID-19 can cause myocarditis on their course, notably. Furthermore, several studies have shown an increasing rate of myocarditis and pericarditis post-COVID vaccination, especially after mRNA-based vaccines (Moderna and Pfizer) [76]. Moreover, the incidence rate of myocarditis after receiving the second dose is twice compared to the first dose, and most cases were reported within 3 days after receiving the vaccine [74,77–81]. Epidemiologically, these events tend to be more common in younger adults and sex distribution showed that the majority of the patients are males [77,78,81–83].

Sulemankhil et al. reported that a 33-year-old male presented with acute substernal pain 2 days after receiving the Ad26.COV.S (Janssen) vaccine. His symptoms started a day after vaccination, starting with myalgia and chills that progressed to non-exertional chest pain. His RT-PCR for SARS-CoV-2 was tested negative, and he was diagnosed with vaccine-induced myocarditis with gadolinium-based magnetic resonance imaging (MRI). The patient underwent symptomatic therapy and stabilization, discharged with no cardiac malfunctioning [84]. Of note, according to the lower risk of myocarditis and pericarditis after adenoviral-based vaccines, Minghui et al. have suggested alternative use of adenoviral vaccines in patients at high risk of myocarditis or pericarditis [85].

4.2. Acute coronary syndrome (ACS)

Acute coronary syndrome (ACS) includes unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) [86]. Jonathan et al. reported two cases of post-COVID-19 vaccination STEMI. The first patient was a 68-year-old female who started having symptoms of left-shoulder pain that later progressed to chest pain within the first day after receiving the first dose of Moderna. The patient tested negative for SARS-CoV-2 RT-PCR. She underwent percutaneous cardiac intervention (PCI) and was discharged after a week only with mild hypokinesis of the anterolateral and inferolateral walls. The next case was a 42-year-old man who started symptoms a few hours after Moderna and presented with 4 days of chest pain. The patient was diagnosed with NSTEMI and underwent emergency PCI and was fully recovered and discharged [87].

A study reported that the risk of ACS after the COVID-19 vaccine increases with age, in contrast to peri-myocarditis, which is more common in younger adults [86,88–90]. ACS is most likely to happen on the first day of vaccination and the incidence decreases by days and after a week, its probability equals that of not vaccinated individuals [86,91]. Several hypotheses, including post-vaccination prothrombotic state due to autoimmune response against platelets [92,93], Kounis syndrome [94], or demand ischemia arising from post-vaccination stress

[95], are put forth to explain the underlying reason. However, further studies are suggested to investigate the relationship, being casual or just a coincidence, between vaccines and ACS.

4.3. Hypertension crisis

Melyan et al. reported nine cases of hypertension crisis (stage III Hypertension) during the first 30 days after COVID-19 vaccination. All cases received mRNA-based vaccines including eight patients receiving Pfizer/BioNTech (BNT162b2) vaccine and a patient with the Moderna vaccine. The sex distribution of patients was seven women and two men, and eight of nine patients had well-controlled hypertension before vaccination. The author suggests several hypotheses to explain the underlying cause of hypertension crisis including stress response to pain besides the white coat effect, body reaction to vaccine components, and interaction between ACE2 and S-protein [96]. Other studies have also reported cases of hypertension crisis after the mRNA vaccine [97].

5. Neurologic side effects

Neurologic complications could be considered a major consequence of COVID-19 vaccination due to possible devastating outcomes that could be divided into serious and non-serious groups. According to data from large-scale studies, headache, cerebrovascular accident (CVA), transverse myelitis (TM), Guillain–Barré Syndrome (GBS), and Bell's palsy are considered the most prevalent neurologic complications. However, some articles have also reported aseptic meningitis, multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), encephalitis, cranial nerve involvement (such as I, VI, VII cranial nerves), seizure, and peripheral neuropathy, which have yet to be validated by controlled and well-designed studies [98,99]. In this section, we review and discuss the neurologic adverse effects of SARS-CoV-2 vaccination reported by the most strong studies.

5.1. Guillain–Barré Syndrome

Guillain–Barré Syndrome (GBS), an immune-mediated polyneuropathy, could happen probably due to molecular mimicry after a precipitating factor, such as vaccination, viral, and bacterial infections. In the era of the COVID-19 pandemic, there have been upcoming reports of GBS following SARS-CoV-2 infection [100,101]. The occurrence of GBS has also been reported after SARS-CoV-2 vaccination. Findings from a study by Osowicki et al. reported an elevation in the incidence of GBS following the ChAdOx1-S vaccine (1.0 cases per 100,000) compared to the background incidence of 0.69 per 100,000 in the adult population. However, they did not receive any reports of GBS following the Pfizer-BioNTech vaccine [102]. It is reported that in the trial of the Johnson & Johnson COVID-19 vaccine, there were two cases of GBS during 2 weeks of incubation, one case in the placebo group and the other one in the vaccine receiving group. Loza et al. concluded that owing to the typical clinical features of both two patients and identical incidence rates of GBS in the placebo and vaccine arms of the trial, there might not be a causal relationship between vaccination and GBS [103]. García-Grimshaw et al. analyzed 3,890,250 Pfizer vaccines over a period of 30 days after vaccine administration. They found that the incidence of the GBS post-Pfizer vaccine was 0.18 per 100,000 and concluded that GBS was not a usual complication of the Pfizer vaccine [104]. Moreover, a study done by Shasha et al. showed similar results [105].

After all, the question that should be answered is whether there is any real causality between SARS-CoV-2 vaccination and GBS or if it is just a temporal co-occurrence. First, if the COVID-19 vaccination could be a cause for GBS, then we expect a higher incidence rate of GBS in the period after vaccination. However, one could say that the elevation in the incidence of GBS following COVID-19 vaccination is masked due to a reduction in non-COVID-19 associated factors causing GBS (such as *Campylobacter jejuni* or respiratory infections) as a result of the lockdown. Second, GBS has a historical incidence rate of 1–2 cases per 100,000 annually [106] and since millions of vaccine doses have already been injected, this means that thousands of GBS cases could be expected. This makes the temporal occurrence of GBS onset and SARS-CoV-2 vaccination more possible [107]. Consistently, Lucchese et al. revealed that there is a high similarity between heat shock proteins 60 and 90 of the human proteome and SARS CoV-2 surface glycoproteins. Since most vaccines include SARS-CoV-2 spike glycoprotein or are engineered to produce it, the same mechanism has been proposed as the underlying reason [108]. To investigate the causality between vaccination and GBS occurrence, large, precise, and well-designed epidemiologic studies are required.

The other question that should be considered is that if there was a previous experience of GBS post-vaccination, what should be done for the future shot? A study by David et al. tried to answer this question [101]. They found that among 702 individuals receiving Pfizer who had a past medical history of post-vaccination GBS from 2000 to 2020, only one case developed GBS after the Pfizer vaccine [109]. Therefore, prior post-vaccination GBS is not a contraindication for vaccination against COVID-19.

5.2. Transverse myelitis

Transverse myelitis (TM) is an immune-mediated spinal cord lesion that causes bilateral sensory, motor, and autonomic deficits below the level of the lesion. There are some reported cases of TM after COVID-19 infection [110]. Temporal associations between TM and vaccination against HBV, HPV, measles-mumps-rubella, pertussis, diphtheria, and tetanus have been previously reported [111]. Similar to other vaccines, several TM cases have been seen after both mRNA and adenovirus-based SARS-CoV-2 vaccines. Several pathomechanisms could be considered for TM, including molecular mimicry, acceleration of current ongoing immune process secondary to the expansion of autoreactive T cells secondary to polyclonal activation of B lymphocytes, and activation of antigen-presenting cells [112,113].

Hirose et al. reported a 70-year-old male presenting with progressive sensory-motor deficit 7 days following injection of

the mRNA-1273 vaccine. Evaluation of patient CSF showed positive oligoclonal body (OGB) which can be suggestive of the autoimmune process including polyclonal activation of B cells [114]. Gao et al. reported longitudinal extensive transverse myelitis (LTEM) in a 72-year-old female after receiving the mRNA1273 vaccine [115]. Borchers et al. study estimated acute transverse myelitis (ATM) incidence of 1.34 to 4.6 cases per million annually in 35–40-year-old adults [110]. Moreover, Shah et al. reported only 119 cases of TM after vaccination during the period between 1985 and 2017 [116]. Furthermore, three cases were reported with signs and symptoms of ATM after vaccination in the ChAdOx1 nCoV-19 (AZD1222) trials. One of these cases was in the control group and another one was further diagnosed as MS. Therefore, there was only one participant diagnosed with possible vaccine-related TM [110,117]. In this study, the similar incidence of TM in control and vaccine groups questions the casualty between AstraZeneca and TM occurrence. The FDA Adverse Event Reporting System (FAERS) has reported only nine cases of TM after the administration of 51,755,447 dosages of the SARS-CoV-2 vaccines until March 2021, which supports our conclusion [118]. The incidence rate of COVID-19-associated TM is 0.5 cases per million, while SARS-CoV-2-vaccination-associated TM is much lower [110]. Further controlled large-scale studies are needed to investigate the actual relevance and potential risk between the COVID-19 vaccine and TM.

Another concern is the administration of the second dose of COVID-19 vaccines in patients who previously developed TM after the first dose. Hsiao et al. reported a case of ATM following vaccination with Oxford-AstraZeneca in which due to major side effects the second dose switched to the mRNA1273 vaccine and no major adverse effect was observed [119]. Therefore, this study suggested that in the case of post-vaccine TM, injection of the second dose from a different class may be safer.

5.3. Headache

Headache is among the most common neurologic complications after the COVID-19 vaccination. 57.5% of individuals vaccinated with ChAdOx1 nCoV-19 had complained of post-vaccination headaches [120]. Gobel et al. intended to define the characteristics and clinical features of headaches after ChAdOx1 nCoV-19 and BNT162b2 mRNA vaccine by using an online questionnaire. The data from the two above studies concluded that post-vaccination headache was mostly bilateral, lasting up to two days, and was moderate to severe [120,121]. Post-vaccine headache description by patients had characteristics of both migraine (such as photophobia, phonophobia, and deteriorating with movement) and tension-type headache (such as pressing quality). Moreover, individuals younger than 55 years old experienced more severe headaches than people above this age [120]. A systematic review and meta-analysis study reviewed 15 clinical trials in phase 1/2 and concluded that muscular and nervous events (e.g. myalgia and headache) were remarkably elevated in the vaccinated group than in the control group [122]. Consistently, in a study assessing the safety and immunogenicity of Oxford AstraZeneca, the authors found that headache was less common in older adults than in younger [123].

5.4. Cerebrovascular accident (CVA)

Cerebrovascular accidents (CVA) are of great importance since they are life-threatening, require immediate hospitalization, and may result in considerable disability [124]. Several cases with the diagnosis of CVA have been reported after COVID-19 vaccination, presenting as cerebral venous sinus thrombosis (CVST), intracerebral hemorrhage (ICH), and arterial ischemic stroke, which are mainly associated with vaccine-induced thrombotic thrombocytopenia (VITT) [99]. The main mechanism of VITT is mentioned in detail in Section 3 and Figure 2. It could also be secondary to vasculitis of the intracranial arteries [125]. A study from Germany evaluated the incidence rate of CVT in 7,126,434 first-dose vaccine recipients. This study demonstrated that the overall incidence rate of CVT 1 month after vaccination was 0.55%, AstraZeneca has the most association with CVT, and VITT was the most possible mechanism [126]. Moreover, ICH is a life-threatening condition with a high mortality rate and has been reported in several sporadic cases after vaccination with AstraZeneca and Pfizer [127,128] but has not been systematically reported by strong studies.

5.5. Cerebral venous sinus thrombosis (CVST)

CVST is a rare manifestation of thrombosis that mostly occurs in young women. CVST was previously reported in COVID-19 patients that were associated with thrombocytopenia [129]. Several studies have reported CVST post-vaccination with both mRNA and adenovirus-based SARS-CoV-2 vaccines [11,130–132]. CVST has been reported mostly after vector-based vaccines including Johnson and Johnson (Ad26. COV2.S) [133] and ChAdOx1 nCoV-19 [58]. The estimated incidence rate in the case of CVST following Johnson and Johnson was about 8.65 per 100,000 [134]. Another study demonstrated that the relative incidence of CVST following the first dose of AstraZeneca was about 8.7 among 15–39-year-old individuals; however, its measure was about 2.2 among 40–64-year-old individuals [135]. A systematic review aimed to review the reported studies of 49 CVST and VITT from 14 articles, of which 19 patients died [136]. Mendes et al. reported a case of a 35-year-old, 23-week-pregnant woman presenting with a severe headache on day 11 after Oxford-AstraZeneca. The following day, her mental status declined to a coma level. Brain CT of the patient showed a temporoparietal transition of the left cerebral hemisphere and left insula and intraparenchymal hemorrhage in the left temporal lobe [137]. Nevertheless, in a large-scale study by Pawlowsky et al., it was found that COVID-19 vaccination was not associated with CVST incidence [138].

Clinical manifestation of vaccine-related CVST may vary from mild to more severe symptoms in some patients including headache, deviation of the buccal rim, visual impairment, giddiness, papilledema, hemiparesis, seizure, motor deficit, altered mental status, and alertness disturbance. Symptoms mostly start within 30 days after injection of the COVID-19

vaccine and most cases are presented with CVST after injection of the first dose. Risk factors for CVST are similar to those for venous thromboembolism that include pregnancy, CNS infection, drugs (such as OCP, and chemotherapy), and chronic conditions (such as thrombophilia, cancer, and autoimmune disorders) [131]. CVST post-SARS-CoV-2 vaccination can occur secondary to hematological disorders including VITT and DIC [50,139]. Nevertheless, some cases were reported with CVST with normal platelet count and negative anti-PF4 antibody [140]. Furthermore, Fan et al. hypothesized that BNT162b2 mRNA vaccine-related CVST may be associated with spike glycoprotein. Spike protein of SARS-CoV-2 might ground immune-thrombotic events through different pathways such as direct activation of platelet, abnormal activation of the alternative complement pathway, and disruption of the blood–brain barrier (BBB) at and endothelial hemostasis [11]. CVST with thrombocytopenia (under 150 × 109/L) and positive HIT ELISA test or positive anti PF4 antibody fulfill the criteria for VITT. Kammen et al. showed that clinical manifestation, therapeutical approach, and outcome of CVST that fulfills VITT criteria are different from CVST that does not fulfill the criteria for VITT. This study demonstrated that patients with CVST post-COVID-19 vaccine fulfilling TTS criteria manifested more severely and had poor outcomes compared to the control CVST group. Moreover, patients with CVST who did not fulfill the criteria for TTS had a similar clinical profile and outcome to the control CVST group [141].

Krzywicka et al. performed a vaccine-based analysis for vaccine-related CVST and reported that CVST that occurs after vaccination with ChAdOx1 nCov-19 has a different clinical profile from CVST that is not related to vaccination. They also observed that the frequency of vaccine-related CVST was lower in the mRNA vaccine and that no thrombocytopenia was reported for patients who were vaccinated with the mRNA vaccine. Moreover, CVST after ChAdOx1 was associated with a higher mortality rate compared to both mRNA and the control group [142].

Considering that patients with CVA may present with mild complaints, it will be more lifesaving if physicians pay special attention event to the mild neurologic complaints after the administration of SARS-CoV-2 vaccines. A reported case of ICH by Mendes et al. is an objective example of this claim [137]. A retrospective cohort study on 537,913 COVID-19 patients by Taquet et al. showed that CVT was significantly higher following COVID-19 infection in comparison to mRNA vaccine recipients [143]. Therefore, vaccination against SARS-CoV-2 should be encouraged because it outweighs the benefits of the vaccine.

5.6. Bell's palsy

Bell's palsy is an idiopathic or suspected viral etiology of acute facial nerve palsy, with an annual incidence of 15–30 per 100,000 people. Bell's palsy has been seen in COVID-19 infection and post-vaccination [144]. Bell's palsy has been observed after distinct types of COVID-19 vaccines, including Pfizer, Moderna, Johnson and Johnson, and CoronaVac [145,146]. The incidence of post-vaccination Bell's palsy was mostly associated with mRNA vaccines, and it was higher than the expected rate in the community [147]. However, the emergency use authorization of Pfizer and Moderna showed that Bell's palsy was an uncommon complication of these vaccines, less likely to exist causality, and needs further and longitudinal follow-up to be evaluated (US Food and Drug Administration (2020) Moderna COVID-19 vaccine emergency use authorization review memorandum. https://www.fda.gov/media/144673/download. Accessed 15 January 2021. U.S. Food and Drug Administration (2020) Pfizer-BioNTech COVID-19 vaccine emergency use authorization review memorandum. https://www.fda.gov/media/144416/download. Accessed 15 January 2021). Consistently, Wan et al. mentioned that Bell's palsy is a rare complication of the COVID-19 vaccines, and they did not find an elevated risk after Pfizer vaccination, as well. However, it should be considered that in their study, an increased risk of Bell's palsy was mentioned for the CoronaVac vaccine [146]. The low risk of Bell's palsy after mRNA COVID-19 vaccines was also mentioned in other studies that found no association between the COVID-19 vaccine and Bell's palsy [148,149]. So, it seems that BP is a rare adverse effect of the SARS-CoV-2 vaccine, and it will respond well to oral corticosteroids.

6. Immunologic, allergic, and autoimmune side effects

Anaphylaxis is the most important autoimmune reactivity after SARS-CoV-2 vaccination. Other autoimmune conditions, such as vasculitis and autoimmune hepatitis, are other important reactions. However, the identification of causality between the vaccine and the occurrence of auto-immune diseases requires further large-scale studies, by excluding patients with prior autoimmune conditions [150]. There are sporadic case reports of inflammatory bowel disease (IBD), including both ulcerative colitis (UC) flare and Crohn's disease, following the COVID-19 vaccine [151]. Moreover, case reports of Henoch Schoenlein purpura (IgA vasculitis) [152], eosinophilic granulomatosis with polyangiitis [153], polyarthralgia, and granulomatosis nephritis [154] have been reported after AstraZeneca, Pfizer, and Moderna [152,155–157], which are very rare and were often associated with the relapse of the preexisting autoimmune conditions [158].

6.1. Anaphylaxis

Allergic reactions might occur secondary to environmental allergens, foods, and medicines, including drugs and vaccines. Allergic reactions can range from mild to more serious forms and even death. However, the systemic and severe type of allergic reaction, also known as anaphylaxis, is a type I hypersensitivity reaction that can occur minutes after vaccine shots. According to data reported by the CDC and the FDA, the incidence rate of anaphylaxis was 2.5 and 11.1 cases per million after receiving the first dose of Moderna and Pfizer, respectively [159,160]. Consistently, a meta-analysis by Greenhawt et al. found that 7.91 cases per million developed anaphylaxis following mRNA-based SARS-CoV-2

vaccines [161]. Another study has recently reported the incidence of anaphylaxis to be 0.3% in partially vaccinated and 0.2% in fully vaccinated individuals [162]. Most of the anaphylactic cases occurred within 30 minutes after mRNA vaccine administration [159,160]. A major number of cases with anaphylaxis had a positive history of allergy. Moreover, about 81% of anaphylaxis cases following the Pfizer vaccine had a previous history of food, medicines, and insect sting allergies. Also, 33% of cases had a history of an anaphylactic reaction [160].

An anaphylactic reaction is more common after mRNA vaccines that is probably due to the adjuvants used. Polyethylene glycol (PEG) is the most probable allergen that might be responsible for anaphylactic reactions after injection of the mRNA SARS-CoV-2 vaccines. Moreover, a similar possible role for polysorbate 80 has been proposed in adenoviral vector SARS-CoV-2 vaccines, as well [163]. Despite the potential role of the PEG in mediating the anaphylactic reactions, the meta-analysis did not support the use of skin allergy tests for individuals with a past medical history of allergy to the COVID-19 vaccine, due to unknown sensitivity and specificity [161].

An important question is that if someone has experienced immediate allergic responses to the vaccine in the first dose, what should be done for the next shot? Krantz et al. revealed that most patients with an immediate anaphylactic reaction after the first dose were able to safely tolerate the second mRNA dose [164]. However, studies have proposed promising and successful desensitization protocols for the mRNA vaccine. By using these protocols, individuals safely tolerated the next shot [165,166]. For individuals who had allergic reactions to the first dose of mRNA SARS-CoV-2 vaccines, changing the platform of the vaccine may reduce the chance of allergic reactions. Consistently, studies supported the idea of switching the platform of the vaccine to the adenoviral vector-based vaccine in individuals who have experienced allergic reactions to the mRNA COVID-19 vaccine [161,167]. Thus, considering the benefits of vaccination outweigh the rare possibility of anaphylaxis and easy management of the anaphylaxis, individuals with a history of unrelated and related allergies should not postpone the vaccination against SARS-CoV-2 [168,169].

6.2. Autoimmune hepatitis

Autoimmune hepatitis (AIH) can be defined as inflammation of liver parenchyma through an autoimmune inflammatory process. AIH arises in genetically susceptible individuals secondary to several triggering factors, such as vaccines [170]. A pattern of autoimmune-like hepatitis is reported in several case reports among people vaccinated by m-RNA and adenovirus-based COVID-19 vaccine both after the first and second doses [151,171,172]. The age of patients ranged from 25 to 74 years old and the time interval between vaccine incubation and presentation of AIH was about 3–46 days [173,174]. Patients with COVID-19 vaccine-related AIH commonly presented with jaundice, pruritus, anorexia, fever, fatigue, malaise, and choluria. However, it should be noted that some cases were asymptomatic and identified in routine follow-up [175]. Common laboratory findings were increased liver transaminases, bilirubin, total IgG, positive Anti-smooth muscle antibody (ASMA), and positive antinuclear antibody (ANA) [171,175]. Tun et al. have reported a case of a 47-year-old male developing AIH after Moderna COVID-19 vaccine incubation. He presented with jaundice and malaise 3 days after first dose of the vaccine, with elevation in bilirubin and ALT with normal albumin and INR. After the second dose of the vaccine, the patient returned with jaundice and deteriorated laboratory findings, an ALT of 1084 U/L, bilirubin 355 µmol/L, and raised prothrombin time (PT). A biopsy of the liver confirmed the AIH diagnosis. The patient responded well to the treatment with 40 mg prednisolone [171]. Although elevated titer of IgG is expected in typical AIH, Brill et al. reported a case of COVID-19 vaccine-related AIH with a normal IgG level [176]. Concomitant with the findings of these studies, the presence of eosinophils in liver biopsy is more commonly suggestive of drug/toxin-induced liver injury rather than AIH [171,176].

Three reasons can be considered for COVID-19 vaccine-related AIH. First, the vaccine may unmask previously existing AIH. Second, vaccines can act as a trigger factor for AIH through molecular mimicry. Lastly, given that the incidence of AIH previously has been reported as about 1 case per 100,000, it can be just a co-occurrence and there may not be a real casualty [177]. Further studies are warranted to clarify the detailed underlying mechanism. The take-home point is that clinicians should be vigilant of the probability of AIH following COVID-19 vaccination since timely treatment is necessary and life-saving.

6.3. Vasculitis

Vasculitis defines the inflammation of blood vessels and is divided into several groups based on the vascular size of affected blood vessels. Although different kinds of vaccines, such as influenza and BCG, have been suspected to induce vasculitis due to their mechanism of action, high-quality studies with a larger number of the statistical population have discovered no relationship between these vaccines and the increasing rate of vasculitis [178,179]. To our knowledge, no large studies have yet investigated the incidence of post-COVID-19 vasculitis; however, ANCA-associated vasculitis and leukocytoclastic vasculitis (LCV) have been commonly reported [180]. Most cases of ANCA-associated vasculitis (AAV) were reported following mRNA vaccines, and they may have caused autoinflammation by activating myeloid and dendritic cells [181–183]. Shakoor et al. reported a 78-year-old female who attended the emergency department with nausea, vomiting, and diarrhea after the second dose of Pfizer-BioNTech. Laboratory results showed increased anti-myeloperoxidase (MPO) and kidney biopsy showed crescentic necrotizing glomerulonephritis. He was diagnosed with post-vaccine AAV and was treated with corticosteroid and rituximab. After being discharged, her serum creatinine level improved from 3.54 at the time of hospitalization to 1.71 during 1 month of follow-up [184].

Leukocytoclastic vasculitis (LCV) is a small-vessel vasculitis caused by nuclear debris from neutrophils and can be idiopathic or due to infections, cancers, autoimmune responses, and drugs [185]. Several studies have reported the occurrence

of LCV after the COVID-19 vaccine [186,187]. As an example, Fiorillo et al. reported a case of LCV in a 71-year-old female 5 days after receiving the second dose of the ChAdOx1 vaccine. The patient presented to the emergency department with burning sensation and skin lesions with purpuric macules and papules on both lower extremities. Biopsy of lesions confirmed the diagnosis of LCV. The patient was started on oral corticosteroids and fully recovered from skin lesions after 14 days [188]. The production of autoantibodies after COVID-19 infection upon release of myeloperoxidase (MPO), proteinase-3 (PR-3), and other immune components by innate immune cells is the main mechanism of post-COVID-19 autoimmune vasculitis [189]. In contrast, SARS-CoV-2 vaccine-induced autoimmunity is generally caused by cross-reactivity to antigen or vaccine adjuvants [190].

7. Conclusion and discussion

Global vaccination against COVID-19 has opened a promising window to overcome the ongoing pandemic [191]. The antiviral immunity empowered by the vaccine is anticipated to produce strong protection against the virus [1]. Among different platforms, viral vector vaccines are more probable of inducing immune-mediated reactions. Based on data from large-scale population-based studies, hematologic adverse effects, including VITT, DIC, CVST, and ITP, are the most commonly reported adverse effects, specifically after the AstraZeneca vaccine [58,136]. Among cardiovascular complications, endo-myocarditis, ACS, and hypertensive crisis have been commonly reported [96,192]. Among post-vaccine neurologic adverse events including GBS, TM, CVAs, headaches, and Bell's palsy are mostly reported [98]. Among immunologic adverse events, anaphylaxis is the most important one which is mostly reported after mRNA vaccines and is probably associated with the immune response against the adjuvant used [159]. Autoimmune hepatitis, vasculitis, and immune-mediated nephrotoxicity are other immunologic adverse effects of the vaccines [70].

Important limitations of the studies exploring vaccine-induced adverse effects must be noted. Since in many cases, the side effect might have been temporally associated with receiving the vaccine rather than causality. Compared to the normal community, the incidence of most of these adverse events is not more probable in the vaccinated community. Moreover, some of these adverse events are even reported to have a higher incidence after COVID-19 infection. Therefore, it seems that the overall benefits of vaccines overweigh the risks and side effects. However, future controlled studies including a large number of vaccine recipients and community-based studies are encouraged since they may reduce the statistical bias. Furthermore, other significant issues must be considered in further studies. First, since the vaccine could act as a precipitating factor for exacerbation/flare of the preexisting disease, patients must be screened to exclude preexisting known and unknown pathologies. Second, the reports of some adverse effects after the second dose probably indicate that the vaccine dosage is an important factor affecting the incidence of these side effects. This is even more important since many countries have started using the booster dose of vaccines and future studies should explore the risk of adverse events after second or booster doses. Third, specific patients from specific groups might be at a higher risk of developing a side effect. In these groups, the appropriate vaccine with the lowest side effects must be administered. As an example, among different vaccines, the risk of thrombotic events and GBS is higher after the Oxford-AstraZeneca vaccine [58,193]. Consistently, based on current data, it seems like there is a causal relationship between thrombotic adverse effects, including CVST and VITT, and the AstraZeneca vaccine. Due to a small number of cases, the causality between the vaccine and other side effects needs further evaluation. To conclude, current studies support that the advantages of the vaccine are greater than the vaccine-associated risks and future studies are still required. More importantly, the occurrence of the new COVID-19 variant, OMICRON, has increased the importance of vaccination to control the pandemic.

8. Expert opinion

Global vaccination against SARS-CoV-2 is currently the most effective strategy to restrain severe disease and hospitalization of COVID-19. Up to now, several vaccine platforms with distinct safety and efficacy profiles have been developed. The most globally used WHO-approved vaccines include mRNA vaccines, including BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), and adenoviral vaccines, including Ad26.COV2.S (Johnson & Johnson) and ChAdOx1nCoV19 (Oxford AstraZeneca), and inactivated vaccines, including Coronavac (Sinovac) and BBIBP-CorV (Sinopharm). Other vaccines of different classes are also under production/investigation, as well.

When using these vaccines to induce an effective immune response, an important issue is the side effect profile of these vaccines. This is necessary to investigate whether the benefits of using the COVID-19 vaccine are greater than the risks imposed. Several factors including age, sex, vaccine type, vaccine dose, allergic history, and previous COVID-19 infection could affect the occurrence of post-vaccine adverse effects. Current studies have reported different post-vaccine side effects. Hematologic, neurologic, cardiovascular, and autoimmune are the four major classes of adverse effects. Major hematologic side effects are VITT, DIC, and ITP. VITT could present with VTE, CVT, PTE, and DVT. The most probable theory for the development of post-vaccine thrombosis is the production of anti-PF4 antibodies; however, it is not the only mechanism since the levels of these antibodies are not elevated in all cases (Figure 2). Cardiovascular side effects, including ACS, HTN crisis, and endo-myocarditis, are very rare but could be life-threatening. GBS is one of the most reported post-vaccine adverse effects; however, the incidence rate of GBS in post-vaccine individuals is not higher than its incidence after COVID-19 infection. Post-vaccine headache is a commonly reported chief complaint; nevertheless, it could be a symptom of more serious pathology, such as CVT. Therefore, the post-vaccine headache should not be neglected, especially if coincident with focal neurologic deficit, which could be indicative of CVA/CVT. Post-vaccine anaphylaxis could progress minutes after vaccination and requires

emergency management. However, other auto-immune side effects, such as hepatitis and vasculitis, can occur after days to months and are often associated with the flare of a preexisting autoimmune disorder rather than a new-onset autoimmune reaction. The incidence of these side effects varies based on vaccine type and the population studied. As an example, thromboembolic events are more prevalent in young females receiving the adenoviral vaccines, especially Oxford-AstraZeneca. On the other hand, autoimmune and anaphylactic reactions are more common after mRNA vaccines, which is probably related to the polyethylene glycol used as the solvent in these vaccines. Altogether, in most cases, the incidence of these adverse events is lower than post-COVID-19 infection.

Moreover, the causality of these adverse events with the vaccine is questioned since it could have been a temporal coincidence in many cases. The results of this article could be empowered by the conduction of a systematic review and meta-analysis study. To our knowledge, our manuscript is the first article that discusses the major side effects of COVID-19 vaccines, and we have included large cohorts, clinical trials, systematic reviews, and community-based published articles. The article '10.1136/bmjopen-2021-050278' entitled 'Side effects of COVID-19 vaccines: a systematic review and meta-analysis protocol of randomized trials' is a protocol article that only includes randomized trials but not cohort and community-based studies. Future large-scale controlled studies are encouraged to evaluate the causality of these events and the mechanisms of each side effect. Such studies could develop reliable risk assessment methods for each side effect using a personalized approach and provide new insights for future vaccine design.

Considering the increased risk of adverse outcomes of pregnancy, such as stillbirth and preterm birth, in SARS-CoV-2 infected mothers, vaccination against SARS-CoV-2 could be beneficial by reducing the advent of these adverse effects in pregnant women [194]. However, the issue that should be addressed is whether SARS-CoV-2 vaccines are safe during pregnancy or not. The dominance of evidence regarding the safety of SARS-CoV-2 vaccination during pregnancy is by mRNA-based SARS-CoV-2 vaccines due to the broad application of this type of vaccine among pregnant individuals [195]. Based on the current data, SARS-CoV-2 vaccination has not been associated with histopathologic alterations in the placenta [196]. Furthermore, the reception of SARS-CoV-2 vaccines has not been associated with a significantly higher risk of poor pregnancy outcomes including stillbirth, preterm labor, being small for gestational age, need for neonatal care admission, and a low Apgar score [197]. Moreover, the rate of vaccine side effects in pregnant individuals who received the Pfizer-BioNTech SARS-CoV-2 vaccine was not different from non-pregnant cases [198]. Altogether, current data support the safety of vaccination against COVID-19 during pregnancy and show that the benefits outweigh the risks.

Children are highly susceptible to COVID-19 due to close contact within the school environment. Therefore, vaccination in children could be lifesaving during a pandemic [81]. However, there is concern about the safety and effectiveness of the vaccine in children that may affect parents' decision to vaccinate their children against COVID-19. The results of vaccine clinical trials for children support that vaccination in children is safe and effectively similar to adults. The result of a clinical trial of the BNT162b2 vaccine in 12–15-year-old adolescents showed great efficacy that was higher than in young adults. They also found no serious adverse effects after being fully vaccinated with two doses of vaccine. Injection site pain, fatigue, and headache were the most reported complications in this age group [199]. Furthermore, vaccination with BNT162b2 in children 5–11 years old showed immunogenicity and efficacy with no vaccine-related adverse effects [200]. Nakazawa et al. reported a case of a 15-year-old boy with no significant past medical history who presented with eyelid edema after 4 days and lower extremities edema 8 days after vaccination with the first dose of BNT162b2. He was therefore diagnosed with nephrotic syndrome based on laboratory findings. He was treated with 60 mg prednisolone and achieved full remission within 12 days with no complications [201]. Up to now, there is no significant evidence that showed that this complication was secondary to the vaccine. Therefore, a further, well-designed study is needed to clarify whether it is just a coincidence or if there is a causal association between this complication and vaccination. A study was designed by Keeling et al. to assess the benefits of vaccination in 5–11-year-olds and 11–17-year-olds in England. The result of the study revealed that vaccination of both age groups could be associated with reduced hospital admission and death [202]. Altogether, the benefits of vaccination in children outweigh any possible vaccine-related adverse effects and it is necessary to better control of COVID-19 pandemic.

Funding

This paper was not funded.

Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

A.E. contributed to the hypothesis, writing the manuscript, and revising the final manuscript before submission. R.E., A.S., A.J.M., A.M., M.J.Y., and P. K. contributed to data gathering, writing the primary draft, and preparing tables and figures. R.E. contributed to the correspondence, revising the manuscript, preparing the final draft, and preparing the table.

Data availability statement

Data will be immediately available upon the reviewer and editor's request.

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