Exploratory Research and Hypothesis in Medicine **2022** vol. 7(1) | 64–67
DOI: 10.14218/ERHM.2021.00033

Opinion

Be Alert to the Risk of Adverse Cardiovascular Events after COVID-19 Vaccination

Tuo Han, Weidong Ma, Yan Zhang and Congxia Wang*

Department of Cardiology, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

Received: July 02, 2021 | **Revised:** August 02, 2021 | **Accepted:** August 16, 2021 | **Published:** August 24, 2021

Abstract

With the global popularization of vaccination against coronavirus disease 2019 (COVID-19), the reports of cases of vaccine-related adverse events are increasing gradually. The most common events are local pain at the injection site and atypical symptoms, such as fever, headache, myalgia, and general discomfort. However, a few people might develop serious cardiovascular complications, such as myocarditis, coronary spasm, and thrombosis. Elderly people and adolescents should be more alert to vaccine-related cardiovascular adverse events due to their underlying chronic comorbidities or compromised immune systems.

According to the National Health Commission of China, as of Aug 14, 2021, inoculations with COVID-19 vaccines in China had exceeded 1.84 billion doses, and the inoculation ratio or coverage is increasing.[1] Due to concern with the pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant, China has initiated vaccination for people >60 years old and adolescents aged between 12 and 17 years old since the middle of July 2021. With the popularization of vaccination, reports of various types of adverse events are increasing, especially the occurrence of cardiovascular events, which should be paid attention to.[2]

Currently, there is a wide variety of COVID-19 vaccines that have been approved for emergency use or are receiving scrutinization worldwide, which includes mRNA, viral vectors, virus-like particles, polypeptides, recombinant proteins, attenuated live viruses, and inactivated viruses.[3] Among them, the mRNA vaccine is of the most concern, which has been reported can cause local allergic reactions at the injection site and atypical symptoms, such as fever, headache, myalgia, and general discomfort, which occur in approximately 60% of subjects following the second inoculation.[4] The Pfizer-BioNTech (BNT162b1) and Moderna COVID-19 vaccines (mRNA-1273) are two of the most widely used mRNA vaccines globally, which enable the delivery of the RNA into host cells to allow the expression of the SARS-CoV-2 S antigen. The vaccines elicit an immune response and produce antibodies that are specific to the SARS-CoV-2 virus to protect against COVID-19.[5] The mRNA-based vaccines have some advantages compared with conventional vaccines due to their high potency, the ability for rapid development, and cost-effective production.[6] They actively induce activation of B cell responses and induce the release of cytokines by activating CD8+ and CD4+ T cells.[6] However, the physiochemical properties of mRNA might influence its cellular delivery and organ distribution, which causes mild to moderate local and systematic symptoms in most people that have been vaccinated, thus shield a shadow on mRNA vaccine when safety and reliability are concerned.[5] Most of the symptoms might be related to the over-production of type I interferons and cytokines in vivo that are promoted by the vaccine.[4]

Currently, the widely used COVID-19 vaccines in China, BBIBP-CorV and CoronaVac, are inactivated viruses vaccines, which quickly and effectively induce an immune response against SARS-Cov-2. In addition, they might provoke a strong inflammatory response, which leads to severe adverse cardiovascular events.[7] Inactivated viruses are attractive due to their ability to present multiple viral proteins for immune recognition. Apart from the S protein, other proteins, such as the N protein, M protein, nonstructural proteins, and accessory proteins, could act as potential antigens for SARS-Cov-2.[5] This raises concerns about whether these unimportant antigens could alter the immune system. In addition, more attention should be paid to the antibody-dependent enhancement (ADE) of SARS-CoV-2 infection, because many severe patients that have COVID-19 frequently exhibited more robust immunoglobulin G (IgG) responses and increased antibodies titers, which are closely linked with worse clinical outcomes.[8,9] Whether these vaccines cause abnormal antibody responses are

Keywords: Coronavirus disease 2019; Vaccine; Adverse events; Elderly; Adolescents.
Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IgG/A, immunoglobulin G/A; ADE, antibody-dependent enhancement; TTS, thrombocytopenia syndrome; IFN, type I interferon; NA, not available; VAERS, US Vaccine Adverse Events Reporting System; CDC, Centers for Disease Control; CVST, cerebral venous thrombosis.
***Correspondence to:** Congxia Wang, Department of Cardiology, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China. ORCID: https://orcid.org/0000-0001-6262-2276. Tel: +86-13892838729, E-mail: wcx622@163.com
How to cite this article: Han T, Ma W, Zhang Y, Wang C. Be Alert to the Risk of Adverse Cardiovascular Events after COVID-19 Vaccination. *Explor Res Hypothesis Med* 2022;7(1):64–67. doi: 10.14218/ERHM.2021.00033.

Table 1. Summary of cardiovascular adverse reactions and incidence rates after COVID-19 vaccination

Authors	Data sources	Vaccines Names	Vaccine Types	Cardiovascular adverse reactions	Incidence Rates
Abu Mouch *et al*.[20]	Case report	BNT162b2 vaccine	mRNA	5 patients presented myocarditis after the second and 1 after the first dose of the vaccine	NA
Chamling *et al*.[24]	EudraVigilance	Pfizer-BioNTech and ChAdOx1 nCoV-19 vaccine	mRNA/ adenovirus-vectored	309 (18–64 years old) reported cases of myocarditis associated with Pfizer-BioNTech, 19 (65–85 years old) with ChAdOx1 nCoV-19 vaccine	NA
Deb *et al*.[25]	VAERS and CDC website	mRNA-1273	mRNA	37 vaccine recipients developed myocarditis related to mRNA-1273 vaccine	NA
Kim *et al*.[26]	Case series	2 received mRNA-1273, and 2 received BNT162b2	mRNA	7 patients with acute myocarditis over 3-months which 4 occurred within 5 days of COVID-19 vaccination	NA
Lai *et al*.[27]	EudraVigilance	ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines	adenovirus-vectored	169 cases of CVST and 53 cases of splanchnic vein thrombosis following ChAdOx1 nCoV-19 vaccination out of 34 million people	5 per million people for CVST and 1.6 per million for splanchnic vein thrombosis
Lai *et al*.[27]	VAERS	Ad26.COV2.S	adenovirus-vectored	6 cases of CVST with thrombocytopenia following the administration of 6.86 million doses	0.87 cases per million doses
Sessa *et al*.[28]	VAERS	Pfizer-BioNTech or mRNA-1273 vaccine	mRNA	68 thromboembolic events out of 13.6 million younger women	1 case per 222,951 vaccinated
Welsh *et al*.[29]	VAERS	Pfizer-BioNTech or mRNA-1273 vaccine	mRNA	15 cases of thrombocytopenia were identified among 18,841,309 doses of Pfizer-BioNTech Vaccine and 13 cases among 16,260,102 doses of mRNA-1273 vaccine	0.80 per million doses for both vaccines

Note: NA, not available; VAERS, US Vaccine Adverse Events Reporting System; CDC, Centers for Disease Control; CVST, cerebral venous thrombosis.

currently uncertain and additional research is required to address the potential damage related to SARS-CoV-2 vaccines.

COVID-19 patients have frequent complications with cardiometabolic diseases, such as hypertension, atherosclerosis, heart failure, and diabetes.[10–12] Populations with the previously underlying diseases are at high risk for infection by SARS-CoV-2 and more severe clinical prognosis.[13,14] Aging is known to influence vaccine immunity. Serum neutralization and levels of binding IgG or immunoglobulin A (IgA) following the first vaccine dose were lower in older groups, with a marked decrease in individuals >80 years old.[15] Of note, sera from participants >80 years old showed lower neutralization potency against the B.1.1.7 (Alpha), B.1.351 (Beta), and P.1. (Gamma) variants and were more probable to lack any neutralization against viruses following the first dose.[15] The frequency of SARS-CoV-2 spike-specific memory B cells decreased in non-responders after the first dose, and the production of interferon-γ and interleukin-2 by CD4 T cells was suppressed in older participants.[15] In addition, approximately 9.7% of patients had COVID-19 combined with diabetes.[16] The expression of ACE2 receptor (total and glycosylated form) in diabetes cardiomyocytes was upregulated, which increased the susceptibility to SARS-CoV-2 infiltration by favoring the cellular entry of the virus.[17] In addition, hyperglycemic status attenuated the efficiency of tocilizumab treatment in diabetic and non-diabetic patients.[18] Early glycemic control might be a suitable therapeutic option to reduce the poor outcomes in hospitalized COVID-19 patients with or without diabetes.[19] The diabetic and hyperglycemic states could confer a reduced response to anti-inflammatory and anti-viral therapies. However, whether there is a similar situation for vaccination in diabetes is remains unclear. Specific measures to boost the vaccine response in the elderly and diabetic populations are warranted.

There are some cases reports on severe adverse events related to the COVID-19 vaccine, such as neuritis, facial nerve palsy, myocarditis, and thrombosis[20–22] Myocarditis is a relatively rare but serious complication of vaccination, which is mostly self-limited but can be life-threatening[23] Recently, reports of vaccine-related myocarditis were mostly related to the mRNA vaccine (Table 1), which lead to unbearable chest pain that occurred soon after inoculation and was accompanied by increased biomarkers for myocardial injury.[20,24–26] Cardiac magnetic resonance imaging shows typical myocarditis symptoms, such as regional dysfunction, late gadolinium enhancement, and elevated native T1 and T2.[26] Thrombosis with thrombocytopenia syndrome (TTS) is one of the serious vaccine-related complications, which mainly occurs in women within 2 weeks of the Chadox1 nCoV-19 or Ad26.COV2.s vaccination.[27] Other vaccines appear to be safe and do not appear to have any disproportional reporting of thromboembolic events or thrombocytopenia.[28,29] Impaired type I interferon (IFN) activity, which is characterized by a lack of IFN-β and low

IFN-α production, and exacerbated inflammatory responses were observed in severe COVID-19 patients.[30] The excessive immune responses that are caused by vaccines might aggravate myocardial ischemia and plaque progression, which results in myocardial injury, and in severe cases might lead to plaque rupture and induce acute myocardial infarction.[31] Due to the incomplete development of the immune system in adolescents, vaccination might lead to secondary myocarditis, cardiomyopathy, arrhythmia, and heart failure.[32] A recent phase I/II clinical trial demonstrated satisfactory safety, tolerability, and immunogenicity of the CoronaVac vaccine in children and adolescents aged 3–17 years, with injection site pain as the most common adverse reaction.[33] However, long-term immunogenicity and safety were not available and need to be tracked carefully. In addition, stress stimuli, such as nervousness during vaccination, could provoke the occurrence of hypertension, myocardial ischemia, and arrhythmia.[34]

Currently, guidelines or statements on the use of COVID-19 vaccines and the prevention of adverse events are increasing. According to the Centers for Disease Control's guidance, vaccination locations should: (1) ensure that necessary supplies are available to manage anaphylaxis, especially sufficient quantities of epinephrine in prefilled syringes; (2) screen potential vaccine recipients to identify people with contraindications and precautions, especially those with cardiovascular metabolic comorbidities; (3) implement recommended post-vaccination observation periods, either 15 or 30 m that depend on each patient's previous history of allergic reactions; and (4) ensure that health care providers can recognize the signs and symptoms of anaphylaxis and other life-threatening events early.[35,36] These measures should be strictly carried out especially in remote communities. Patients should seek immediate medical care when they developed signs or symptoms, such as unmitigated chest tightness and palpitations during or after the observation time ends.[37] Physicians in clinics should be alert to the possibility of vaccine-related cardiovascular events, such as myocarditis. Evaluation that includes emergency electrocardiograms and myocardial injury biomarker screening is necessary and echocardiography if available. When TTS is highly suspected or confirmed, consultation with hematology is recommended. The treatment might include intravenous immunoglobulin and anticoagulation and should avoid heparin-based agents and platelet transfusion.[38] Finally, it is essential to relieve the nervousness emotion and assist subjects to perform health management in their daily life, avoid drastic fluctuations in blood pressure or blood glucose, and insist on the primary prevention of cardiovascular diseases during vaccination. In addition, rare and serious adverse events after the COVID-19 vaccination highlight the importance of establishing a sound vaccine safety monitoring system. National regulatory authorities should establish formal trans-regional cooperation to promote data sharing on vaccine safety.[2]

Acknowledgments

The opinions expressed here are solely those of the authors, and not of their affiliations.

Funding

Supported by a grant from the National Science Foundation of China (NO.81273878) and Natural Science Foundation of Shaanxi Province (NO.2021JQ-409).

Conflict of interest

The authors declared no conflict of interests.

Author contributions

HT and MWD conceptualized and wrote the manuscript. ZY and WCX were responsible for the critical revision and supervision.

References

[1] National Health Commission, PRC. COVID-19 vaccine inoculation (in Chinese, updated August 14, 2021). Available from: www.nhc.gov.cn. Accessed August 14, 2021.
[2] Lo Re V 3rd, Klungel OH, Chan KA, Panozzo CA, Zhou W, Winterstein AG. Global covid-19 vaccine rollout and safety surveillance-how to keep pace. BMJ 2021;373:n1416. doi:10.1136/bmj.n1416.
[3] Lai CC, Chen IT, Chao CM, Lee PI, Ko WC, Hsueh PR. COVID-19 vaccines: concerns beyond protective efficacy and safety. Expert Rev Vaccines 2021:1–13. doi:10.1080/14760584.2021.1949293.
[4] Sprent J, King C. COVID-19 vaccine side effects: The positives about feeling bad. Sci Immunol 2021;6(60):eabj9256. doi:10.1126/sciimmunol.abj9256.
[5] Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou F. A systematic review of SARS-CoV-2 vaccine candidates. Signal Transduct Target Ther 2020;5(1):237. doi:10.1038/s41392-020-00352-y.
[6] Wang F, Kream RM, Stefano GB. An evidence based perspective on mRNA-SARS-CoV-2 vaccine development. Med Sci Monit 2020; 26:e924700. doi:10.12659/msm.924700.
[7] Beig Parikhani A, Bazaz M, Bamehr H, Fereshteh S, Amiri S, Salehi-Vaziri M, *et al*. The inclusive review on SARS-CoV-2 biology, epidemiology, diagnosis, and potential management options. Curr Microbiol 2021;78(4):1099–1114. doi:10.1007/s00284-021-02396-x.
[8] Zhang B, Zhou X, Zhu C, Song Y, Feng F, Qiu Y, *et al*. Immune phenotyping based on the neutrophil-to-lymphocyte ratio and IgG level predicts disease severity and outcome for patients with COVID-19. Front Mol Biosci 2020;7:157. doi:10.3389/fmolb.2020.00157.
[9] Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, *et al*. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. Clin Infect Dis 2020;71(16):2027–2034. doi:10.1093/cid/ciaa344.
[10] Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, Covic A. Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones. BMC Geriatr 2021;21(1):389. doi:10.1186/s12877-021-02316-5.
[11] Sardu C, Marfella R, Maggi P, Messina V, Cirillo P, Codella V, *et al*. Implications of ABO blood group in hypertensive patients with covid-19. BMC Cardiovasc Disord 2020;20(1):373. doi:10.1186/s12872-020-01658-z.
[12] Sardu C, Maggi P, Messina V, Iuliano P, Sardu A, Iovinella V, *et al*. Could anti-hypertensive drug therapy affect the clinical prognosis of hypertensive patients with COVID-19 infection? Data from Centers of Southern Italy. J Am Heart Assoc 2020;9(17):e016948. doi:10.1161/jaha.120.016948.
[13] Sharifi Y, Payab M, Mohammadi-Vajari E, Aghili SMM, Sharifi F, Mehrdad N, *et al*. Association between cardiometabolic risk factors and COVID-19 susceptibility, severity and mortality: a review. J Diabetes Metab Disord 2021:1–23. doi:10.1007/s40200-021-00822-2.
[14] Sardu C, Gargiulo G, Esposito G, Paolisso G, Marfella R. Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19. Cardiovasc Diabetol 2020;19(1):76. doi:10.1186/s12933-020-01047-y.
[15] Collier DA, Ferreira I, Kotagiri P, Datir RP, Lim EY, Touizer E, *et al*. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 2021;596:417–422. doi:10.1038/s41586-021-03739-1.
[16] Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, *et al*. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020;109(5):531–538. doi:10.1007/s00392-020-01626-9.
[17] D'Onofrio N, Scisciola L, Sardu C, Trotta MC, De Feo M, Maiello C, *et al*.

Glycated ACE2 receptor in diabetes: open door for SARS-COV-2 entry in cardiomyocyte. Cardiovasc Diabetol 2021;20(1):99. doi:10.1186/s12933-021-01286-7.
[18] Marfella R, Paolisso P, Sardu C, Bergamaschi L, D'Angelo EC, Barbieri M, *et al*. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes Metab 2020;46(5):403–405. doi:10.1016/j.diabet.2020.05.005.
[19] Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, *et al*. Hyperglycaemia on admission to hospital and COVID-19. Diabetologia 2020;63(11):2486–2487. doi:10.1007/s00125-020-05216-2.
[20] Abu Mouch S, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, *et al*. Myocarditis following COVID-19 mRNA vaccination. Vaccine 2021;39(29):3790–3793. doi:10.1016/j.vaccine.2021.05.087.
[21] Tsilingiris D, Vallianou NG, Karampela I, Dalamaga M. Vaccine induced thrombotic thrombocytopenia: The shady chapter of a success story. Metabol Open 2021;11:100101. doi:10.1016/j.metop.2021.100101.
[22] Narasimhalu K, Lee WC, Salkade PR, De Silva DA. Trigeminal and cervical radiculitis after tozinameran vaccination against COVID-19. BMJ Case Rep 2021;14(6):e242344. doi:10.1136/bcr-2021-242344.
[23] Keinath K, Church T, Kurth B, Hulten E. Myocarditis secondary to smallpox vaccination. BMJ Case Rep 2018;2018:bcr2017223523. doi:10.1136/bcr-2017-223523.
[24] Chamling B, Vehof V, Drakos S, Weil M, Stalling P, Vahlhaus C, *et al*. Occurrence of acute infarct-like myocarditis following COVID-19 vaccination: just an accidental co-incidence or rather vaccination-associated autoimmune myocarditis? Clin Res Cardiol 2021;1–5. doi:10.1007/s00392-021-01916-w.
[25] Deb A, Abdelmalek J, Iwuji K, Nugent K. Acute Myocardial Injury Following COVID-19 Vaccination: A Case Report and Review of Current Evidence from Vaccine Adverse Events Reporting System Database. J Prim Care Community Health 2021;12:1–5. doi:10.1177/21501327211029230.
[26] Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, *et al*. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol 2021:e212828. doi:10.1001/jamacardio.2021.2828.
[27] Lai CC, Ko WC, Chen CJ, Chen PY, Huang YC, Lee PI, *et al*. COVID-19 vaccines and thrombosis with thrombocytopenia syndrome. Expert Rev Vaccines 2021:1–9. doi:10.1080/14760584.2021.1949294.
[28] Sessa M, Kragholm K, Hviid A, Andersen M. Thromboembolic events in younger women exposed to Pfizer-BioNTech or Moderna COVID-19 vaccines. Expert Opin Drug Saf 2021:1–3. doi:10.1080/14740338.2021.1955101.
[29] Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2021;39(25):3329–3332. doi:10.1016/j.vaccine.2021.04.054.
[30] Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, *et al*. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020;369(6504):718–724. doi:10.1126/science.abc6027.
[31] Liu J, Virani SS, Alam M, Denktas AE, Hamzeh I, Khalid U. Coronavirus disease-19 and cardiovascular disease: A risk factor or a risk marker? Rev Med Virol 2021;31(3):e2172. doi:10.1002/rmv.2172.
[32] Raghavan S, Gayathri R, Kancharla S, Kolli P, Ranjitha J, Shankar V. Cardiovascular Impacts on COVID-19 Infected Patients. Front Cardiovasc Med 2021;8:670659. doi:10.3389/fcvm.2021.670659.
[33] Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z, *et al*. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021. doi:10.1016/s1473-3099(21)00319-4.
[34] Kongbundansuk S, Hundley WG. Noninvasive imaging of cardiovascular injury related to the treatment of cancer. JACC Cardiovasc Imaging 2014;7(8):824–838. doi:10.1016/j.jcmg.2014.06.007.
[35] Shimabukuro T. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine - United States, December 14-23, 2020. Am J Transplant 2021;21(3):1332–1337. doi:10.1111/ajt.16516.
[36] CDC. Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States (updated August 13, 2021). Available from: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed August 14, 2021.
[37] Kim MA, Lee YW, Kim SR, Kim JH, Min TK, Park HS, *et al*. COVID-19 vaccine-associated anaphylaxis and allergic reactions: consensus statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group. Allergy Asthma Immunol Res 2021;13(4):526–544. doi:10.4168/aair.2021.13.4.526.
[38] Long B, Bridwell R, Gottlieb M. Thrombosis with thrombocytopenia syndrome associated with COVID-19 vaccines. Am J Emerg Med 2021;49:58–61. doi:10.1016/j.ajem.2021.05.054.