International Journal of Gerontology 16 (2022) 180–185
https://doi.org/10.6890/IJGE.202207_16(3).0003

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Review Article

Stroke Related to COVID-19 Infection and Vaccination – A Review

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ARTICLE INFO

Accepted 21 April 2022

Keywords:
COVID-19,
stroke,
vaccine

SUMMARY

Since December 2019, the emergence of coronavirus disease 2019 (COVID-19) has had a major impact worldwide. This emerging virus does not only affect the respiratory system but also affects the nervous system. Cerebrovascular events have been reported as complications of COVID-19. In this review article, we summarized the epidemiology, stroke subtype, characteristics, laboratory findings, pathophysiology, risk factors and treatment of stroke in COVID-19 patients by reviewing case reports and cohort studies. On the other hand, sporadic adverse events such as systemic thromboembolism and stroke have been reported after COVID-19 vaccination. Herein, we reviewed the literature to elucidate the association between COVID-19 vaccines and stroke with the aim of assisting clinical decisions and giving people greater confidence in receiving vaccines.

1. Introduction

Since December 2019, the emergence of coronavirus disease 2019 (COVID-19) has had a major impact worldwide. According to the data from CDC of Taiwan, by March 2022, there were 435 million infections and 5.97 million deaths occurred due to COVID-19 infection all over the world. COVID-19 does not only affect the respiratory system, but also affects the nervous system. Common neurological symptoms, including headache, hyposmia, hypogeusia, dizziness, and less commonly, seizures, encephalopathy, and acute cerebrovascular disease have been reported.[1,2] This is a new disease in which we have very little knowledge in relation to cerebrovascular disease. In this review article, we summarize the characteristics of stroke patients with COVID-19 infection by searching case reports and cohort studies.[3–19] At the same time, the development of vaccines against COVID-19 has allowed us to see a glimmer of hope. As we speed up the development of vaccines, safety is the topmost priority. However, there have been sporadic reports about vaccine related adverse events and death that reduce the willingness to receive vaccines.[20] Could we convince everyone that the benefits outweigh the side effects under the currently available evidence? Herein, we review literature to elucidate the association between COVID-19 vaccines and stroke with the aim of assisting clinical decisions and giving people greater confidence in receiving vaccines.

2. Epidemiology of stroke in COVID-19 infection

In currently published cohort studies, the incidence of COVID-19 infection complicated by stroke (including ischemic and hemorrhagic) is approximately 0.5–5%.[3] A meta-analysis that included 24 studies and a total of 108,571 people reported that the pooled incidence of stroke was 1.4% which varied by region, ranging from 1.1% to 1.2% in North America and Europe and 3.1% in Asia.[3] Men are more likely to experience stroke with COVID-19 than women.[3–8]

However, there is an inconsistency in the reported conclusions regarding whether the incidence of stroke is higher in COVID-19-infected patients than in the general population. In one study using the U.S. Cerner Real-World database, 103 (1.3%) of 8,163 COVID-19-infected patients developed ischemic stroke, while 199 (1.0%) of 19,513 patients who were not infected with COVID-19 had ischemic stroke.[9] No obvious difference in stroke incidence between the two groups was noted in this observational study. On the other hand, another British study using the national registry of COVID-19 vaccination to carry out a self-controlled case series study, including a total of 1,758,095 COVID-19 positive patients, found that the incidence of ischemic stroke within 28 days of infection was 1.26–3.94 times higher than the baseline.[10] The severity of the COVID-19 infection also affects the risk of stroke. In a meta-analysis, the odds ratio of stroke is 5.10 (95% CI: 2.72–9.54) in severe COVID-19 infection.[3] Even in asymptomatic COVID-19 infection, the incidence of stroke is higher than general population. In a case series study in Singapore, 15 stroke patients were reported in a cohort of 54,485 South Asian workers living in the dormitories, who were laboratory-confirmed asymptomatic COVID-19 infection. Their annual incidence rate of ischemic stroke was higher compared with historical matched cohort (82.6 vs. 38.2 per 100,000, OR: 2.16, 95% CI: 1.36–3.48).[21]

Whether COVID-19 infection increases ischemic stroke remains to be clarified, but there is evidence that COVID-19-related stroke is characteristically different from a traditional stroke with cerebrovascular risk factors.

3. COVID-19 can cause ischemic stroke in younger age

Some studies did not show differences in age between stroke

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patients with and without COVID-19. In a case-control study in UK that included 1,470 stroke cases, the median age of stroke patients with and without COVID-19 infection was 74.5 and 73 years old, respectively, with no significant statistical difference.[5] Another cohort study of 27,676 people, the mean age of acute ischemic stroke with and without COVID-19 were similar (68.8 vs. 71.0, p = 0.24).[9] But in most studies, the median age of stroke associated with COVID-19 infection is between 62.5–67.2 years old, which is younger than the cases of ischemic stroke without COVID-19 infection.[4,11,12] A retrospective cohort study in New York, US, documented 32 patients with ischemic stroke who were positive for COVID-19 with a significantly lower median age than those of with ischemic stroke who were negative for COVID-19 (63 vs. 70, p = 0.001).[6] Another meta-analysis found a similar result that the pooled median age difference was six years younger in stroke with COVID-19 infection (-6 years, 95% CI: -12.3~-1.4).[3] These patients also had less cerebrovascular risk. In one meta-analysis, young (< 50 years old) ischemic stroke patients with COVID-19 infection were the ones most likely to have no cerebrovascular risk factors, and they had the lowest frequency of hypertension, atrial fibrillation, and coronary artery disease compared to those > 50 years old.[7] This may hint that COVID-19 possesses an obscure mechanism for ischemic stroke; thus, these young patients are often classified as having cryptogenic stroke. To explore the mechanism between COVID-19 and ischemic stroke, further stroke subtype classification is required.

4. Subtype of ischemic stroke with COVID-19 infection

In a systemic review of 160 cases of stroke after COVID-19 infection, the results showed that among all stroke subtypes, ischemic stroke was the most common (78.8%), followed by intracerebral hemorrhage (15%), cerebral venous thrombosis (4.4%), and subarachnoid hemorrhage (1.9%).[5] Another multinational cohort study involving 432 patients showed roughly the same proportions, except that subarachnoid hemorrhage was slightly higher than cerebral venous thrombosis (5.3% vs. 4.2%).[12]

Many patients with ischemic stroke and COVID-19 have demonstrated large vessel occlusion (LVO) on vascular imaging. Previous case series and systemic reviews reported about 41–46.9% of patients were found to have LVO,[5–7,12] which is higher than that of ischemic stroke without COVID-19 infection.[3,13] Furthermore, a study in UK also showed that the rate of multi-territory LVO increased significantly in stroke with COVID-19.[5] The finding of multifocal LVO may hint a unique mechanism of stroke in COVID-19 infection, such as inflammation-related hypercoagulable status, diffuse vascular endothelium damage, or heart injury-induced cardioembolism, rather than common atherosclerosis and small vessel disease. In clinical practice, COVID-19-infected patients may present with LVO but lack an obvious risk factor for stroke. Therefore, in the TOAST classification, cryptogenic stroke accounts for 22.4–44.7%, while small vessel disease accounts for only 2–10%.[3,8,11,12,14]

The consequences of LVO are reflected in the severity of stroke, with significantly higher mean National Institute of Health Stroke Scale (NIHSS) scores in COVID-19-positive patients.[22] In a cohort study in New York, the median NIHSS score of COVID-19-positive stroke patients was higher than that of COVID-19-negative stroke patients (19 vs. 8, p = 0.007).[6]

5. Laboratory findings in ischemic stroke with COVID-19 infection

In contrast to common pneumonia and viral influenza, COVID-19 causes severe inflammation and immune responses; therefore, systemic complications are significantly more frequent. The laboratory findings showed that the C-reactive protein (CRP) and D-dimer levels of stroke patients with COVID-19 were higher than those of stroke patients without COVID-19,[5] suggesting that the mechanism of stroke caused by COVID-19 may be related to the hypercoagulable status in severe inflammation. D-dimer levels may also be correlated with the severity of COVID-19 infection and can be used as an indicator of poor outcomes.[15]

Some case series found antiphospholipid antibodies, including anticardiolipin antibody, anti-B2-glyocprotien, and lupus anticoagulant, in the serum of stroke patients with COVID-19.[4,16] Antiphospholipid antibodies are associated with a predisposition for blood clots in the arteries or veins. However, acute infections are sometimes associated with transient positive antiphospholipid antibodies, and the prevalence of positive antiphospholipid antibodies in the general healthy population is still unknown. To date, no well-designed large trials have compared whether stroke patients with COVID-19 have higher antiphospholipid antibody titers. Therefore, the significance of antiphospholipid antibodies in the pathogenesis of COVID-19 associated stroke still warrants further investigation.

6. Prognosis of ischemic stroke with COVID-19 infection

The mortality rate of ischemic stroke in COVID-19 positive patients is about 19–38%, which is significantly higher than that in COVID-19 negative patients.[3,5,9,14] A meta-analysis showed that the odds ratio of in-hospital mortality of ischemic stroke in COVID-19 positive was 5.21 (95% CI: 3.43–7.90) compared with COVID-19 negative.[3] The cohort study in New York reported 14 deaths among 22 stroke patients with COVID-19 positive, with an abnormally high mortality rate of 63%.[6] This study was conducted at the peak of the epidemic in New York between March and April 2020, with 3,000–4,000 new patients infected every day. In terms of medical exhaustion at that time, these deaths may be related to sepsis or respiratory failure caused by COVID-19 itself and fewer medical resources allocated to stroke care. However, evidence has shown a more advanced stroke severity and poorer functional outcomes in stroke survivors with COVID-19. In the UK cohort study results, the median mRS on discharge was higher in COVID-19 positive patients (4 vs. 3, p < 0.0001).[5] Multiple organ damage and more serious neurological deficits caused by COVID-19 may lead to more neurological sequelae.

7. Pathophysiology of ischemic stroke with COVID-19 infection

Combining the above-mentioned characteristics of COVID-19-associated stroke, such as the lack of traditional vascular risk factors, multiple LVO, higher inflammatory index and D-dimer, higher stroke severity, and poorer prognosis, scientists speculate that the mechanism of stroke caused by COVID-19 is different from traditional stroke. The pathogenesis is still incompletely understood, and there may be many contributing factors related to the acute inflammatory response to COVID-19 infection (Figure 1).[3,17]

7.1. Sepsis-induced hypercoagulation

COVID-19 causes a more severe inflammatory response than general pneumonia or other viral influenza. One cohort study at two hospitals in New York compared the characteristics and stroke rates of patients with COVID-19 and influenza virus infection. They found a higher rate of ICU admission (25% vs. 6%), mechanical ventilation

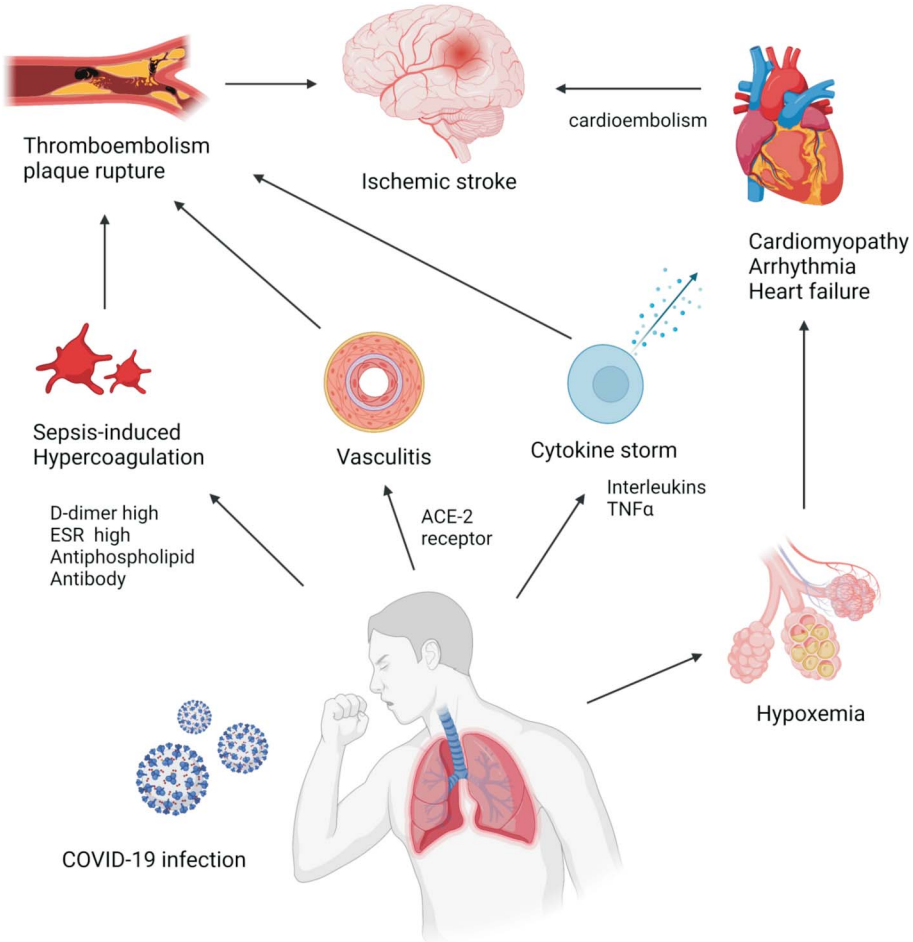

Figure 1. Overview of the possible mechanism of ischemic stroke in COVID-19 infection. Figure created with BioRender.com. ESR, erythrocyte sedimentation rate.

(17% vs. 3%), and higher D-dimer and erythrocyte sedimentation rate (ESR) in COVID-19 positive patients. The likelihood of acute ischemic stroke was higher with COVID-19 infection than with influenza infection (adjusted odds ratio 7.6, 95% CI: 2.3–25.2).[18] The severe infection may cause sepsis-induced coagulopathy which explains the reason for D-dimer elevation. Antiphospholipid antibodies might also play a role in sepsis-induced hypercoagulation. Ischemic stroke may develop through direct artery occlusion or venous thrombosis with a paradoxical embolus. This also explains the finding of LVO in young patients without any vascular risk factors.

7.2. Cytokine storm

In COVID-19 infection, several cytokines, including IL2, IL6, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα have been found to be markedly elevated.[19] In those with severe disease, this response is exaggerated, resulting in a "cytokine storm". Cytokines have numerous pro-inflammatory and pro-coagulant effects on the endothelium, activating the coagulation pathway, and evidently causing blood clotting. Besides, cytokines are also involved in the atherosclerotic plaque development and rupture.[23]

7.3. Vascular endothelium injury

COVID-19 infects the host via the ACE-2 receptor, which is likely to cause direct damage to the vascular endothelium. The ACE-2 receptor is mainly expressed in the lungs, heart, kidneys, and vascular endothelium. COVID-19 infection may cause vasculitis and trigger platelet aggregation or rupture of the superimposed plaque. Patients with pre-existing arteriosclerosis are at a higher risk of stroke after infecting with COVID-19.[1,7]

7.4. Severe hypoxemia

Many COVID-19 patients present with profound hypoxemia without signs of respiratory distress, in which rapid deterioration may occur. In the first few days of the disease, lung function was preserved; thus, the respiratory center did not trigger hyperventilation. However, rapid respiratory decompensation may occur, causing hypoxic damage to the brain and heart, especially in patients with carotid artery stenosis and coronary artery disease.

7.5. Cardiomyopathy

Cardiac involvement may be caused directly by COVID-19 virus invasion due to the affinity of the ACE-2 receptor, which is abundant in heart tissue, leading to myocardial dysfunction. It is also indirectly affected by systemic inflammation, cytokine storms, and hypoxemia. This may lead to arrhythmia and heart failure and increase the risk of cardioembolic stroke.

8. Ischemic stroke risk factors in COVID-19 infection

Although there are special stroke mechanisms in patients with COVID-19, traditional vascular risk factors still play a role in predisposing patients to ischemic stroke. A meta-analysis found that older

age (+4.8 years), hypertension (OR = 7.35, 95% CI: 1.94–27.87), diabetes (OR = 5.56, 95% CI: 3.34–9.24), and coronary artery disease (OR = 3.12, 95% CI: 1.61–6.02), all reached statistical significance and contributed to ischemic stroke in COVID-19 positive patients.[3] Another retrospective cohort study had similar results, showing that older age, the incidence of hypertension, diabetes, hyperlipidemia, atrial fibrillation, and congestive heart failure were significantly higher in patients with ischemic stroke in COVID-19 positive patients.[9] These remind us that traditional stroke risk factors still play an important role, and COVID-19 may be a trigger factor in these already high-risk populations. In public health policy, these high-risk populations for stroke should be given more delicate preventive measures, such as vaccination.

9. Treatment for ischemic stroke with COVID-19 infection

Intravenous thrombolysis and endovascular thrombectomy should be provided for eligible stroke patients under the premise of safety. Stroke societies had promulgated criteria for selection of patients for intravenous thrombolysis and endovascular thrombectomy according to the local epidemic prevention policy.[24–26] The benefit and necessity of stroke intervention should be weighted with the safety of medical crews, the risk of infectious spreading, and the capacity of healthcare resources. Stroke team members should have appropriate personal protective equipment. However, reduced efficacy of thrombolysis and thrombectomy had been reported, which may relate to multiple vessel occlusion, larger clot burden and clot fragmentation.[27,28]

It is still not clear whether antiplatelet or anticoagulant provide superior efficacy in primary or secondary stroke prevention with COVID-19 infection. Because of the evidence of hypercoagulable status and cardiomyopathy in COVID-19 infection which may be responsible for stroke, experts recommend low molecular weight heparin (LMWH) as thromboprophylaxis in all COVID-19 hospitalized patients, particularly those with severe infection or high D-dimer level.[29–32] However, anticoagulant should be used with caution in acute phase of ischemic stroke, as it might raise the risk of hemorrhagic transformation. Using anticoagulant seems reasonable in selected patients such as multi-territory infarction suggesting embolic stroke, small infarction size, positive antiphospholipid antibody, high D-dimer level, and critical ill patients who require mechanical ventilation that have higher risk for systemic thrombosis and pulmonary embolism.[33]

10. COVID-19 vaccine and stroke

In response to the COVID-19 epidemic, vaccines against COVID-19 have been authorized for marketing since December 2020. The development of vaccines was accelerated to fight the global pandemic; thus, post-marketing safety surveillance is of high importance. A few months after widespread vaccination, adverse reactions have been reported. The most well-known adverse event was that the recombinant adenovirus vector vaccine (AstraZeneca ChAdOx1 nCov-19, Johnson & Johnson/Janssen Ad26.COV2.S) may cause venous thrombosis with thrombocytopenia (Table 1). This vaccine-induced thrombotic thrombocytopenia (VITT) may be similar to heparin-induced thrombocytopenia (HIT), which is caused by triggering an abnormal immune response that produces antibodies against platelet factor 4 on platelet surface.[34,35] Autopsy and histological research also showed the expression of adhesion molecule VICAM-1 and complement components C1r and C4d on the vascular endothelium, along with the CD163 and CD66b-positive inflammatory cell, indicate the activation of the immune system that promote inflammatory process.[36,37] Most patients developed symptoms within 5 to 30 days of vaccination. The most common thrombotic site is cerebral vein and sinus, accounting for 50%, followed by pulmonary embolism and deep vein thrombosis of legs (37%). There were also unusual thrombosis in veins such as splanchnic vein, portal vein, ophthalmic vein, jugular vein, and in many cases, multiple veins.[38] In a German study of these post-vaccination venous thrombosis cases, women accounted for the majority (77.8%) of the patients, and they were younger than 60 years old (80%). ChAdOx1 was nine times more likely to develop cerebral venous thrombosis than the mRNA vaccine.[39] Due to the successive case reports of venous thromboembolism, many European countries announced the pause of the ChAdOx1 injection program or additional age limitation for ChAdOx1 injection after April 2021.

Most of the adverse thrombotic events after vaccination were venous embolisms; however, there were also some case reports of arterial embolism. A British cohort study of patients with VITT estimated that arterial embolism accounted for 12% of all adverse events.[38] In previous case reports, cerebral artery embolism after vaccination occurred mostly in young patients (< 60 years old) with no obvious risk factors. The onset of ischemic stroke is usually between 7 and 21 days after vaccination. The embolism occluded large arteries and sometimes in bilateral hemispheres simultaneously.[40–45] Systemic venous embolism was often detected in ischemic stroke patients at the same time, including the cerebral venous sinus, portal vein, pulmonary artery, and ophthalmic vein. Blood tests showed a low platelet count (< 100,000/cm^3) and positive anti-platelet factor 4 antibody with a diagnosis of VITT. Most patients received intravenous immunoglobulin (IVIG), plasmapheresis, and anticoagulant therapy. If the patients present to the hospital within the time window, they may receive thrombolysis therapy; however, due to concomitant thrombocytopenia, these patients are usually not candidates for intravenous thrombolysis. Instead, most patients had large artery occlusion in the setting of VITT, so they had the opportunity to undergo intra-arterial thrombectomy. Patients who successfully achieved recanalization and received subsequent intravenous immunoglobulin, plasmapheresis, and anticoagulant therapy showed improvement in platelet count and better recovery from stroke.[44] Conversely, those with re-occlusion, hemorrhagic transformation, and multi-territory infarction often had poor outcomes.[40,43,45]

Whether COVID-19 vaccine increases the chance of ischemic

Table 1
Incidence of thromboembolic events following vaccination.

Study	Vaccine	Event	Sample size	Incidence
Schultz et al.,[35] (Norway)	ChAdOx1	TTS	130,000	3.8 per 100,000 injections
See et al,[48] (US)	Ad26.COV2.S	TTS	14,100,000	0.38 per 100,000 injections
	mRNA-based	TTS	351,000,000	0.00086 per 100,000 injections
Schultz et al,[39] (Germany)	ChAdOx1	CVT	2,320,535	1.52 per 100,000 person-month
	BNT162b2	CVT	4,454,505	0.11 per 100,000 person-month
UK MHRA report on 10 March 2022[49]	ChAdOx1	TTS	24,900,000	1.75 per 100,000 injections

CVT, cerebral venous thrombosis; MRHA, Medicines & Healthcare products Regulatory Agency; TTS, thrombosis with thrombocytopenia syndrome.

stroke is currently limited to case reports and large cohort studies. Randomized control trials are still lacking. A Danish and Norwegian cohort study included 281,264 people who received the ChAdOx1 vaccine and observed the incidence of arterial and venous thromboembolisms. They found that total cerebral infarction was not higher than the expected background incidence (incidence ratio 0.92, 95% CI: 0.53–1.50), but intracerebral hemorrhage was significantly increased by two times (incidence ratio 2.33, 95% CI: 1.01–4.59), and cerebral venous sinus thrombosis was significantly increased by 20 times (incidence ratio 20.25, 95% CI: 8.14–41.73). Despite the significant increase in the risk of cerebral venous sinus thrombosis, the absolute incidence rate is still only 1–2/100,000-person year, which is a rare complication of vaccination.[46]

Another UK study, using the national registry of COVID-19 vaccination to carry out a self-controlled case series, included a total of 19,608,008 individuals with ChAdOx1 vaccine, 9,513,625 individuals with BNT162b2 vaccine, and 1,758,095 patients with COVID-19 positive.[10] To compare the incidence rates of arterial or venous thromboembolic events in these three groups, this study observed the stroke events within the exposure period (21 days after vaccination or COVID-19 infection), and then conducted a self-comparison with the baseline period (29 days before and after exposure period) as the control group. The results showed that ischemic stroke risk slightly increased after ChAdOx1 (incidence rate ratio 1.07 on day 8–14) and BNT162b2 (incidence rate ratio 1.12 on day 15–21) vaccination; the risk of cerebral venous thrombosis increased in both vaccines (ChAdOx1 incidence rate ratio 4.01 on day 8–14 and BNT 162b2 incidence rate ratio 3.58 on day 15–21). Nevertheless, the risk of ischemic stroke and cerebral venous thrombosis after vaccination is still far less than COVID-19 infection (incidence rate ratio of ischemic stroke 2.00 to 3.94 on day 1–21, and cerebral venous thrombosis 12.9 to 13.4 on day 1–14). Therefore, experts recommend that people without a history of special diseases should receive the vaccine, because the benefits far outweigh the risk of these rare adverse events.[47] If there is a history of coagulopathy such as autoimmune disease, cancer, heparin-induced thrombocytopenia, deep vein thrombosis, cerebral venous sinus thrombosis, idiopathic thrombocytopenic purpura, perhaps an mRNA-based vaccine is a better choice.

11. Conclusion

According to the currently published literature, the probability of stroke within 30 days after infection with COVID-19 is approximately 0.5–5%, and some studies have suggested that infection with COVID-19 will increase the risk of ischemic stroke and lower the onset age of stroke. Ischemic strokes in patients infected with COVID-19 are mainly manifested by LVO and even in multiple territories; therefore, the severity of stroke was more severe, with more neurological sequelae and higher mortality. However, the mechanism that caused LVO is often obscure; therefore, cryptogenic stroke (undetermined) was the most common subtype in TOAST classification. Current research suggests that the mechanism is related to the severe inflammatory response and hypercoagulation state caused by COVID-19 infection. After being infected with COVID-19, people with traditional cerebrovascular risk factors, including high blood pressure, hyperlipidemia, heart disease, and older age, have a higher risk of developing stroke. Therefore, from a public health perspective, people with a history of stroke or a high risk of cerebrovascular disease should be vaccinated. When people hear reports that COVID-19 vaccine can cause blood clots, they often worry about strokes, especially in patients who have already experienced a stroke. They may be hesitant on receiving a vaccine or question which brand of vaccine they should choose. In fact, the existing vaccines against COVID-19, whether adenovirus vector-based or mRNA-based vaccines, all had case reports of adverse reactions of artery or venous thromboembolism, but statistically, the incidence of ischemic stroke is extremely low (approximately 1 in 10,000) and the risk has only increased slightly (1.07 to 1.12 folds),[10] which is much lower than the probability of stroke after COVID-19 infection. To minimize the occurrence of vaccine-related adverse events, physicians should obtain a detailed medical history prior to vaccination. If there is a coagulation disorder, mRNA-based vaccines may be less likely to cause VITT. If there is an unexplained ischemic stroke or cerebral venous sinus thrombosis, doctors should be more aware of the vaccination history. Blood cell count and serum anti-platelet factor 4 antibody tests can be helpful in confirming the diagnosis of VITT. Intra-arterial thrombectomy has been reported to be safe and effective for VITT with large vessel occlusion. Treatment with intravenous immunoglobulin, plasmapheresis, and anticoagulant therapy may be helpful for patients with VITT.

Declaration

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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