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Review Article

COVID-19 and Blood Clots: Is it only The Virus to be Blamed? What are new Updates? A Systematic Review

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Abstract

COVID-19 is a viral disease that infected most of the people on the planet as a pandemic. The disease is attributed to the SARS-CoV-2 virus, which causes respiratory symptoms, vascular disorders and can infect more body systems. This article aims to expand the list of causes of blood clotting as well as to focus the light on the links between blood clots and the virus which was always blamed to cause thrombosis. From the literature, reasons of blood coagulation consist of 3 main categories: non-infectious, infectious, and medications. Some medications used in the international therapeutic protocol for COVID-19 might cause blood coagulation such as zinc, glucocorticoids, and favipiravir which are not well studied. Finally, new causes of thrombosis are recently added to the list which are SARS-CoV-2, some therapeutics used for COVID-19 treatment strategy, and COVID-19 vaccines. In conclusion, SARS-CoV-2 may cause blood clots, but it is not the only reason. COVID-19, some medicines used to treat patients, and COVID-19 vaccines are added to the list of causes of blood clots despite the rare incidence of blood clots recorded in vaccinated people.

Keywords: COVID-19; Blood clots; Pulmonary venous thromboembolism (VTE); Glucocorticoids; Favipiravir.

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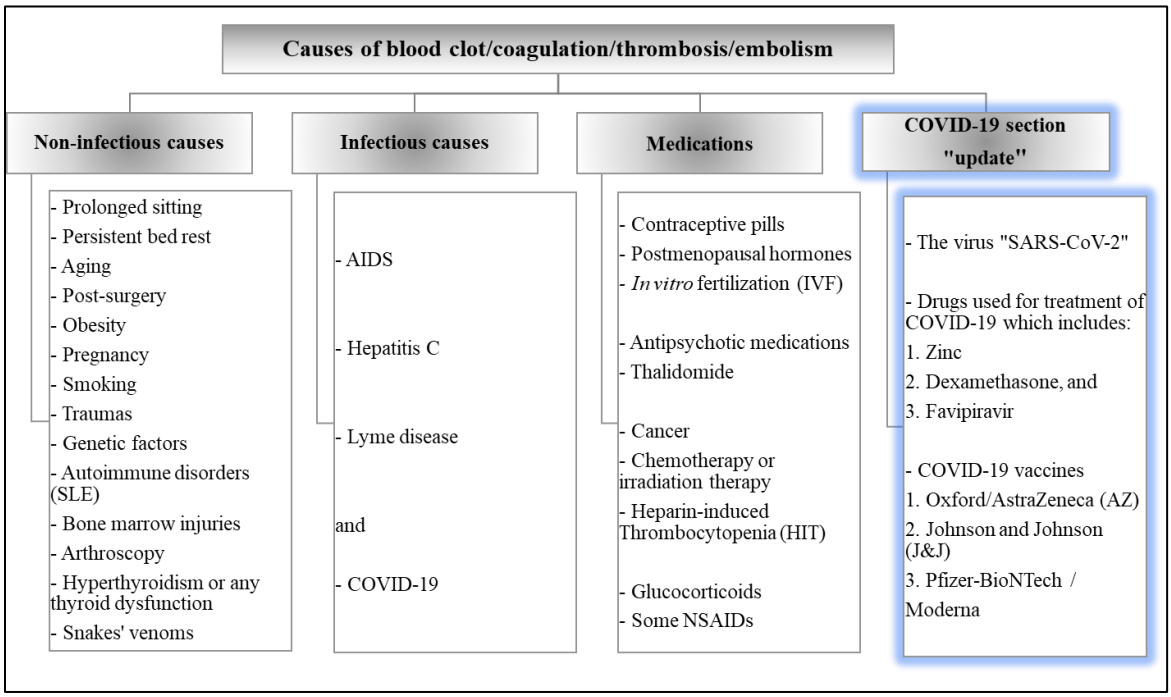
Graphical abstract



Introduction

COVID-19 is a viral disease caused by the SARS-CoV-2 virus, an RNA virus that is known to cause respiratory symptoms in most patients globally [1,2], and has a major impact on the cardiovascular system causing blood clots [3,4], in addition to its ability to target other body systems such as digestive system [5], urinary system [6,7], skin [8], genital organs [9], eyes [10] and both central and peripheral nervous system [11]. This virus is reported to cause a sharp increase in blood viscosity, consequently raising the chance of blood clot formation leading to a state of hypoxia (dropped oxygen level) which requires further oxygen supply through mechanical ventilators. The incidence of blood clots among COVID patients is variable. For example, in a study done in the USA, the incidence of thromboembolism was 18.2% and 14.2% in the non-cancer and the cancer cohort patients respectively [12], while Dutch hospitals recorded proportional thrombotic rates approached 12% after 10 days, 16% after 20 days and 21% after 30 days in the ICU patients [13] but jumped to 31% thrombotic cases in the ICU patients in other Dutch hospitals [14] (Table 1). This article aims to explain to what extent blood clot is caused by the virus. Is there something else to be blamed or the virus only should account for all blood clots of COVID-19 patients? What are the causes of blood clots? This article does not explain in detail the mechanism of each cause because they were already discussed in the literature. The focus is further applied to the recent causes of blood clots, medications used for the treatment of COVID-19 that caused blood coagulation, and how that was linked to the

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virus which confused most physicians who dealt with COVID-19 patients.

Case definitions from medical dictionaries

Blood clot (blood coagulation): gel-like collections of blood that resulted from platelets and fibrin in either veins or arteries changing blood from a liquid to semi-solid.

Embolism: closure of a blood vessel by an extrinsic material or a mass of clotted blood that circulates via the bloodstream, lodging in any part of a blood vessel causing partial or complete plugged vessel.

Thrombosis: blockage of blood vessels by blood clots

Thromboembolism: any floating clot or thrombus formation in a blood vessel carried by the bloodstream to plug another vessel.

See online sources for these dictionaries: Mosby's Medical Dictionary, Dorland's Illustrated Medical Dictionary, Merriam-Webster Medical Dictionary, and Oxford Medical Dictionary.

Causes of blood clot coagulation thrombosis embolism

A few scientists were interested in putting the list of causes of blood clots. The latest article was published in 2016 which listed only causes of venous thrombosis [15]. Below is a general list of the main causes of blood clots divided into four categories.

Non-infectious causes of blood clotting

Blood clot (blood coagulation), thrombosis, or embolism is mostly attributed to non-infectious reasons such as prolonged sitting represented by watching television, spending hours on smartphones or computers, long-lasting trip, or due to an absence or lack of physical exercise for whatever reason [16-18]; persistent bed rest due to chronic illness, aging, post-surgery or for whatever reason [19-21]; obesity [22-24]; pregnancy [25-27] and smoking [28-30].

Moreover, severe traumas may cause venous thrombosis [31-33]. Genetic factors also might be linked to blood clotting [34-36]. Autoimmune disorders (mainly systemic lupus erythematosus, SLE) are listed as one of the causative agents of blood coagulation [37-40]. Bone marrow injuries result for some reason in blood coagulopathy simply because hematopoiesis (biosynthesis of blood cells including thrombocytes) occurs in the bone marrow [41].

For example, myeloproliferative disease may cause venous thrombosis [42]. Arthroscopy is also one of the applications that may increase the risk of blood coagulation, especially knee arthroscopy [43]. Finally, hyperthyroidism or any thyroid dysfunction may induce venous thrombosis [44]. Snakes venoms are classified as hemotoxic (besides other properties such as neurotoxic, cytotoxic, necrotic, nephrotoxic, and myotoxic) as described in the literature [45,46].

The hemolytic effect of snakes' venom on the blood (blood thinner/anticoagulant activity) leads to massive destruction of RBCs and platelets causing internal hemorrhage because of the phospholipases A2 activity [47,48], serine proteases [49], or metalloproteinases [50]. In contrast, snakes'

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venoms were found to induce the formation of blood clots for 9 decades ago [51] by triggering the zymogen pathway, one of the thrombosis factors, or by conversion of soluble fibrinogen in the blood into a non-soluble fibrin plug [52,53]

Infectious causes of blood clotting

Acquired immunodeficiency syndrome (AIDS) is an illness mediated by the human immunodeficiency virus (HIV) discovered more than 3 decades ago [54]. HIV is known to possess immunosuppressive activities causing lymphopenia (specifically a sharp decrease in CD4+ T cells) in addition to targeting the cardiovascular system causing thrombosis [55-59]. To date, no vaccine nor effective therapy is available yet for this viral disease.

Hepatitis C is another viral disease infecting liver of individuals globally resulting in chronic liver diseases characterized by chronic inflammation of the liver (hepatitis, from which the name was derived) with an overall reduction in body immune defense mechanisms due to impairment of protein synthesis in the liver [60-62]. Hepatitis C virus was reported to cause venous thromboembolism (VTE) in most patients at the late stages of the disease [63,64]. Neither a vaccine nor effective treatment is available yet for this viral disease.

Lyme disease is a bacterial infectious disease attributed to spirochetes, a bacterium named "Borrelia", a tick-borne disease targeting skin, neurons, and heart [65-67]. This bacterium infects cerebrum causing venous microthrombi in chronic and complicated cases and was reported as a cause of coronary artery thrombosis in postmortem analysis [68-70].

Medications accused to cause blood clotting

There are more causes of blood clots related to some medications that may induce thrombosis through platelets adherence and subsequent thrombi formation due to direct damage of endothelial and exposure to the underlying subendothelium also can affect white and red cells [71]. Contraceptive pills are one of the medications that may promote thrombosis by altering the balance between the different coagulation factors [71-74], hormonal therapy mostly estrogen or its derivatives [75-78], and postmenopausal hormones in elder women [79].

In addition, in vitro fertilization (IVF) was attributed to venous thrombosis in women [80]. Antipsychotic medications (mainly olanzapine and risperidone) are also reported to cause venous thrombosis [81-85]. Moreover, Thalidomide was recognized as one of the most important causes of induced venous thrombosis [86]. Furthermore, some cases of blood clotting may evolve during cancer especially in women because of anti-cancer drugs (chemotherapy or irradiation therapy) or due to progressive breast cancer itself [87-89].

Chemotherapeutic agents including 5-fluorouracil (5-FU) [90, 91], Doxorubicin [92], Gemtuzumab ozogamicin [93], Tamoxifen [94] are all attributed to cause blood coagulation. Paclitaxel when hypersensitivity immediate response and chronic inflammatory condition, leading to stent thrombosis due to its administration with

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drug-eluting stents [95]. Antagonists of vascular endothelial growth factor (VEGF) such as bevacizumab led to endothelial cell apoptosis, subsequently terminated by arterial and/or venous thrombosis [96,97]. Immunosuppressive agents including Ciclosporin and Sirolimus, and Interferon-alpha can lead to thrombosis and thrombotic microangiopathy (TMA) by inducing disturbances in the microcirculation [98-100]. Intravenous immunoglobulin through arterial vasospasm and enhance blood viscosity, which is mostly possibly terminated with thromboembolism [101,102].

Immunotherapy with recombinant human granulocyte colony-stimulating factor (G-CSF) was thought to enhance levels of endothelial markers and significance increased d-dimer resulted in prolonged thrombin time [103]. Heparin-induced thrombocytopenia (HIT) occurs as an immunological response to exogenous heparin intravenous administration leads to form and synthesis of unwanted immunoglobulins towards platelet factor 4 (PF_4) and intrinsic heparin. These risky antibodies attach to FcγRIIA receptor on thrombocytes to make them aggregate together causing plugging clots [104].

Anti-inflammatory medications such as glucocorticoids are responsible for pulmonary embolism (PE) and deep vein thrombosis (DVT) but this is not quite common [105,106]. Furthermore, some of the non-steroidal anti-inflammatory drugs (NSAIDs) are responsible for aggregations of thrombocytes (platelets). Coxibs are an example of NSAID that enhanced clotting formation through inhibiting cyclooxygenase-2 (COX-2) affecting thromboxane biosynthesis, the major determinant of platelet aggregation [107]. In contrast, acetylsalicylic acid (Aspirin) is known as an anticoagulant through inhibiting prostaglandin formation by targeting COX-1 enzyme pathway [108,109] and this is why it is advised as one of the most common NSAID medications as an anticoagulant. Erythropoietin (EPO) can enhance blood viscosity which leads to blood clotting due to an increase in red blood cell mass.

In addition to its ability in changing the balance between vasodilatory and vasoconstrictive prostaglandins due to increased vascular resistance leads to endothelial cell and platelet activation [110]. Metformin induces hyperhomocysteinemia that leads to oxidative damage to the endothelial cells, thus raising the chance of blood clotting in diabetic individuals [111]. Sildenafil under phosphodiesterase (PDE) inhibitors classification causes vasodilating properties that may cause blood stagnation and venous thrombotic symptoms [112].

Contrast media (Iodinated-type) used in radiology (angiography) lead to endothelial injury and platelet adhesiveness suggesting that contrast media with low-osmolar or iso-osmolar lower prone to induce thrombosis and that was reported as one of the adverse effects as reviewed in the literature [113].

COVID-19 vaccines account for blood clots as an adverse side effect

An update has been recently added this year (2021) to the list of causes of blood clots. It is the adverse effect(s) of COVID-19 vaccines. Although these are reported as rare cases,

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these vaccines seem to cause blood coagulation in all age groups, both genders. Blood coagulation was mostly connected to the problematic adverse effects of vaccinated individuals with Oxford/AstraZeneca (AZ) plus Johnson and Johnson (J&J) or the so-called Janssen vaccine [114]. Both AZ and J&J use vector-method vaccines which means using adenovirus as a holder for the spike protein of SARS-CoV-2 (the virus that causes COVID-19 pandemic) see manufacturers' websites for both vaccines. This method triggered formation of harmful autoantibodies that have anti-platelet factor 4 (PF4) properties [114]. More recently published articles have confirmed the actual link between AZ and J&J vaccines with thrombosis/embolism cases among vaccinated people [115-119]. Both Pfizer-BioNTech and Moderna vaccines use mRNA technology, a modern method for delivering vaccines used for the first time in the world in humans [120]. These mRNA vaccines are also thought to cause thrombosis, but the mechanism is not well understood [121-123]. It seems like all COVID-19 vaccines may cause thrombosis which was described as vaccine-induced immune thrombotic thrombocytopenia (VITT), an acronym used for the first time in the world [122,124-126]. The worse scenario is that blood clots were reported in vaccinated children [127]. Approval of a new blood thinner for children aged 3 months to 11 years by the FDA (dated in August 2021 in coincidence with the plan to vaccinate children with COVID-19 vaccines) is a warning sign for possible progression of blood clots in this age group, which is the possible scenario to what is happening to children vaccinated with COVID-19 vaccines in the near future [128] and this is why this review article is written to update the list of causes of blood clots.

Does SARS-CoV-2 "fully" account for blood clots?

SARS-CoV-2 caused increasing blood viscosity (indicated by d dimer, a small size protein fragment that is made when a blood clot dissolves in the body, normal range concentrations should not exceed 0.5 μg/ml) and many reports of pulmonary venous thromboembolism (VTE) confirmed its relationship to blood clot formation [129-133]. However, this paper is questioning whether pulmonary VTE cases were all attributed to SARS-CoV-2 only, or was there something else that cause VTE?

Medications in the international therapeutic protocol for COVID-19 caused thrombosis

Zinc

International therapeutic protocol for COVID-19 included some medications that have a direct link to the induction of blood coagulation. Zinc is an important element for the immune response, prescribed by approximately all physicians, plays an essential role in thrombocytes' functioning and the process of thrombosis [134-136]. The daily body requirement of zinc is 8 mg and 11 mg for adult women and men respectively according to Mayo Clinic but can be increased a bit higher to boost the immune system [137]. Physicians prescribed 50 mg per day during the COVID-19 pandemic and that is 4 to 5 times more excess than required. Zinc overdose is one of the main causes of

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pulmonary VTE because of the overstimulation of thrombocytes.

Steroid

Dexamethasone, a glucocorticoid, or a steroid anti-inflammatory therapy is prescribed for severe and critically ill patients to inhibit cytokine storm [138,139]. Not to ignore the fact that steroids, mainly glucocorticoids are responsible for pulmonary embolism and deep vein thrombosis [105,106]. More side effects of glucocorticoids particularly symptoms and side effects on the cardiovascular system with a focus on myocardial infarction and stroke consequently their impact on the initiation of VTE which is still arguable as reviewed in the literature [140]. Cushing's syndrome gives an indication of a possible link between exogenous glucocorticoid administration and cardiovascular disorders including a high chance of blood coagulation confers a piece of evidence that exogenous steroids are in charge of increasing the chance of VTE [141], which might be applied to COVID-19 patients [142].

Moreover, exogenous glucocorticoids cause generalized muscle weakness, tiredness, and fatigue as well-known side effects. This muscular wasting (both cardiac and skeletal muscles) results in low cardiac blood-pumping activities, which in turn slows down circulation and increases the risk of pulmonary VTE [143-146]. Furthermore, steroids are one of the most immunosuppressive medications that destroy the immune system by killing leucocytes [147], which gives a bigger space for SARS-CoV-2 to overcome or evade weakened immune cells and attack blood vessels causing more blood clots than expected, i.e., steroid doubles or triples probability of blood coagulation due to viral over-reactivity as a result of immunosuppression (this an opinion of the authors). One more disastrous side effect of steroids is temporary hyperglycemia which impairs the function of all body cells due to a lack of glucose intake. This applies pleiotropic effects on body cells including all types of blood cells (RBCs, WBCs, and platelets), thus cardiovascular disorders are one of the affected systems in COVID-19 patients [148].

Favipiravir (Avigan@)

Last but not least, favipiravir (Avigan@) 200 mg is a prodrug and an antiviral medication used previously to treat viral diseases such as Ebola and influenza and recently prescribed by the vast majority of physicians for COVID-19 cases [149-151]. Adverse effects of this drug included blood and lymphatic illnesses, cardiovascular issues, hepatobiliary dysfunctions, injury poisoning, uremia, and gastrointestinal disturbances such as emesis, diarrhea, and nausea [152,153].

Just to focus on blood, blood vessels, and heart because of adverse effects of favipiravir. These side effects were not studied except one study showed erythrocytopenia [154]. Clinical observations and notes released by physicians revealed that most favipiravir-treated COVID-19 patients suffered from a prolonged massive elevation of d dimer (from 2 to 4 μg/ml or occasionally up to 8 μg/ml) after recovery despite they were on anticoagulant therapy (heparin, rivaroxaban, enoxaparin, clopidogrel or any other anticoagulant). This

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situation stays up to 30 days post-recovery as patients followed up and requested to do d dimer test. Therefore, urgent clinical trials or investigational studies are essentially needed to evaluate the hematological parameters and blood clot formation as adverse effects of favipiravir therapy.

Mahmood's therapeutic protocol vs the international therapeutic protocol for COVID-19

To compare between COVID-19 patients treated with favipiravir who suffered from prolonged higher levels of d dimer post-recovery and patients treated with Mahmood et al [155] protocol, all recovered COVID-19 patients who followed Mahmood's protocol did not record elevated d dimer values (all within normal range, below 0.5 μg/ml). The reasons behind these differences might be attributed to the use of natural anticoagulants in Mahmood's protocol. These natural blood thinners used in Mahmood's protocol are basically garlic which contains allicin that works on COX-1 pathway [156-160], medicinal plants such as turmeric or its active ingredient "curcumin" [161,162], cinnamon [163,164], and ginger [165,166]. Finally, there are more reasons for blood clotting all mentioned in sections: non-infectious causes of blood clotting), infectious causes of blood clotting and medications accused to cause blood clotting, thus it is not the virus alone (SARS-CoV-2) which is to blame for VTE, there is a long list of reasons as mentioned above.

Mechanism of thrombosis

The mechanism of thrombosis has been fully explained in the literature. Microcirculation (blood capillaries; arterioles and/or venules) coagulation was initially discussed for more than 5 decades [167]. Later on, several studies came through the process of blood clot formation which was mostly linked to thrombin antagonists for whatever reason or disturbances in any of the 12 clotting factors [168].

Thrombi in cancer patients might go through special pathways which were fully described and reviewed by [169]. Rates of thrombosis have been dramatically increased since the COVID-19 pandemic. Spike protein of SARS-CoV-2 virus was known to infect and target the endothelial layer of blood vessels (both arteries and veins, plus their branches) causing coagulations in addition to particular damage to the endothelium of blood vessels which is attributed to angiotensin-converting enzyme-2 (ACE-2) receptor through tissue plasminogen activators activation, platelet dysfunction and thrombotic microangiopathy, complement activation, cytokine storm, hypoxia-inducible factors and hypoxia, or anti-phospholipid antibodies all discussed and reviewed by [170] who explained the deadliest type of blood clots in COVID-19 patients "cerebral thrombosis" and that was further expanded to include all possible thrombosis mechanisms in COVID-19 patients which were covered up with diagrams and sketches and reviewed by [171].

Incidence of thrombosis

Thrombosis may happen on both arterial and venous sides of the body. Below are two tables for the occurrence rates of thrombosis in the COVID-19 patients as well as COVID-19 vaccinated individuals.

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Description of thrombotic COVID-19 patients	Type (V/A)	%	Ref
Thromboembolism in non-cancer and the cancer ICU patients, USA.	A	18.2%, 14.2%	[12]
Thromboembolism after 30 days in the ICU patients in Dutch hospitals was recorded at two waves of infections.	V A	23%, 35% 3.1%, 5.6%	[13]
PE, DVT, and systemic arterial embolism in the ICU patients in Dutch hospitals	Mixed	31%	[14]
Thrombosis in hospitalized patients (both ICU and non-ICU), USA.	Mixed	16%	[172]
COVID-19 patients who were on mechanical ventilators showed DVT, USA	V	36%	[173]
PE (mostly venous type) in the ICU patients in Dutch hospitals	Mixed	87%	[174]
DVT in critically ill patients with COVID-19, China.	V	46%	[175]
PE in the COVID-19 patients diagnosed with pneumonia: overall cases and ICU, France	V	24%, 50%	[176]
Thromboembolism in the ICU patients at 7, 14, and 21 days, Netherlands	V	16%, 33% and 42%	[177]
DVT in hospitalized patients, China	V	46.1%	[178]
DVT in non-ICU patients, Spain	V	16%	[179]
VTE of a systematic review included 36 studies on the ICU patients	V	28% (pooled)	[180]
VTE of a systematic review included 23 studies on the general wards and ICU patients	V	14.7%, 23.4% (pooled	[181]

Table 1: Incidence of thrombosis in the COVID-19 patients.
PE= Pulmonary embolism, DVT= deep-vein thrombus, V= venous, A= arterial, Ref= reference

Description of thrombotic COVID-19 vaccinated individuals	Type (V/A)	No. of cases	Ref
Thrombosis including CVST reported to the UK MHRA	V	79 incl 44	[182]
CVT including VITT in Germany	V	45 incl 26	[183]
Thromboembolism recorded by WHO VigiBase reporting system	Mixed	2161	[184]
Thrombosis and CVT reported globally	Mixed	17, 169,	[185]
TTS cases in the USA reported by the CDC	Mixed	15	[186]

Table 2: Incidence of thrombosis in the COVID-19 vaccinated individuals.
CVST or (CVT)=cerebral venous sinus thrombosis, MHRA=Medicines & Healthcare Products Regulatory Agency, VITT=vaccine-induced immune thrombotic thrombocytopenia, TTS=thrombosis with thrombocytopenia syndrome, CDC=Centers for Disease Control and Prevention.

There were many published papers with rare cases of thrombosis after COVID-19 vaccinations. These are not representing the huge number of thrombotic-vaccinated people who visit cardiologists and hematologists' clinics and hospitals every day. There may be a lack of documentation or some other reasons. It is not reasonable that

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FDA limited Janssen (J&J) vaccine due to rare cases of TTS (https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-janssen-covid-19-vaccine-certain-individuals). Moreover, AstraZeneca (AZ) was halted in many European countries (https://apnews.com/article/germany-suspends-astrazeneca-vaccine-blood-clotting-0ab2c4fe13370c96c873e896387eb92f) due to the high rate of blood clots although these were reported as rare cases in the literature. For example, Denmark completely stopped the rollout of AZ (https://www.bbc.com/news/world-europe-56744474). These blood clots are sometimes considered as a life-threatening event that caused many individuals to avoid taking the boosters despite their rare incidence. For this reason, Mahmood suggested better alternatives for these vaccines [187].

Conclusion

COVID-19 pandemic caused by SARS-CoV-2 was always blamed for causing blood clots. This article listed the most possible reasons and causes of blood clots including medications used in the international therapeutic protocol for COVID-19. The virus alone may cause blood clots but there are also many other causes ignored or skipped that need attention. The virus (SARS-CoV-2), remedies used for the treatment of COVID-19, and its vaccines are all added to the list of causes of blood clots. The list is now updated, and this is the scientific touch of this article.

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Conflicts of Interests

The authors declare no competing interests.

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