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Review article

VASCULAR COMPLICATIONS IN LONG COVID ARE VERY RARE

VASKULARNE KOMPLIKACIJE KOD SINDROMA PRODUŽENOG COVID-A SU JAKO RETKE

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Abstract

Depending on the methodology thrombotic events during the acute COVID-19 infection were noted from 20 - 85%. Following the acute phase of the disease, it was noted that a subgroup of patients had various non-specific, prevailing symptoms for weeks, or even months and such a condition was accepted as a long COVID. Having in mind mechanisms of vascular complications in acute COVID infection and pathogenesis of long COVID, one would expect similar presentation and consequences of long COVID on human vasculature.

We conducted a wide search of the literature on the topic and after screening of titles and abstracts papers with potential inclusion of the data regarding long COVID and vascular symptoms or complications that occurred during the time span of more than then 4 weeks after COVID infection.

Research dealing with long COVID are mostly focused on symptoms and laboratory findings due to the nature of this condition. Data regarding vascular complications in these studies are either missing or the incidence of vascular complications was very low. Very few manifestations were related to cardiovascular system and D-dimer was assessed in only two studies showing increased values from very lot to almost in 30% of patients after COVID infection. Finally, in comparison of vascular complications with other viral infections in Sweden on patients undergoing diagnostic tests for venous thromboembolism increased risk for VTE in COVID-positive patients was proved. In the group of patients with chronic cardiovascular disease, the risk of arterial and venous thrombotic events after COVID infection is substantially higher. In comparison with seasonal influenza burden with coagulation disorders, pulmonary embolism, acute phlebitis, thrombophlebitis or thromboembolism and arterial embolism were higher and cumulative incidence was reported from 0.6 - 5.5% while hazard ration was from 2 - 18.

Based on the published literature, vascular complications in the long COVID are very rare. Comparing to a very high rate of thrombotic events in the acute COVID infection and their correlation with severity of clinical presentation of COVID infection, the role and presence of vascular complications in long COVID is without any significance. Future studies focusing on the pathophysiology of long COVID could probably reveal potential mechanisms and explanations for such a difference.

Keywords:
vascular complications,
thrombosis,
ischemia,
pulmonary embolism,
vein thrombosis,
arterial thrombosis,
emoblisation,
long COVID

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Sažetak

U zavisnosti od metodologije tromboze tokom akutne infekcije COVID-om su zabeleženu u 20 - 85% bolesnika. Nakon akutne faze, određena grupa pacijenata ima različite simptome nespecifične prirode koji mogu trajati i mesecima, te se takvo stanje naziva produženim COVID-om. Imajući u vidu mehanizme nastanka i učestalost vaskularnih komplikacija tokom COVID infekcije kao i patogenezu produženog COVID-a, očekivali bi da i ovde dominiraju trombotski procesi kako na arterijskom, tako i na venskom sistemu.

Sproveli smo opsežni pregled literature tražeći naučne radove koji opisuju trombotske, arterijske, ili venske komplikacije u produženom COVID sindromu, više od četiri nedelje nakon akutne epizode. Istraživanja koja se bave produženim COVID-om su uglavnom fokusirana na simptome i laboratorijske rezultate, dok rezultati koji se bave trombotskim komplikacijama uglavnom nedostaju ili su retke. Jako je malo kardiovaskularnih manifestacija, dok su vrednosti D-dimera procenjivane u samo dve studije. Jedna od malobrojnih istraživanja koja poredi efekte drugih virusnih infekcija i COVID-a je pokazala da je u produženom COVID-u učeastalost trombotskih komplikacija nešto veća. Posebno je osetljiva grupa hroničnih kardiovaskularnih bolesnika kod kojih je učestalost trombotskih događaja znatno veća.

Vaskularne komplikacije produženog COVID-a su retke u dostupnoj literaturi, posebno u poređenju sa ulogom trombotskih događaja u akutnoj COVID infekciji. Buduća istraživanja će, nadamo se, pokazati uzrok i potencijalne mehanizme za ovakvu razliku.

Ključne reči:
vaskularne komplikacije,
tromboza,
ishemija,
pulmonarni embolizam,
venska tromboza,
arterijska tromboza,
embolija,
produženi COVID

Introduction

During the acute COVID-19 infection, thrombotic events were very frequent and their prevention was one of the most important targets of therapy in both hospitalized and ambulatory patients (1, 2). Initially, they were reported in the intensive care unit (ICU) in up to 30% of patients (3). Later on, thrombotic events also occurred in patients with mild clinical presentations, related to catheters or manifested in different scenarios like acute myocardial infarction, upper or lower extremity embolization, stroke and thromboembolic events related to deep vein thrombosis (4). Furthermore, in studies that screened critically ill patients with COVID-19 for thrombotic disease, the incidence ranged from 69% to 85% despite thromboprophylaxis (5, 6).

The disease has taken a huge toll worldwide ever since its outbreak, and the pathogenic mechanisms that contribute to pulmonary and extra-pulmonary manifestations of acute SARS-CoV-2 viral infection have been thoroughly studied. Following the acute phase of the disease, it was noted that a subgroup of patients has had various non-specific, prevailing symptoms for weeks, or even months. National Institute for Health and Care Excellence (NICE) summarized the post-COVID symptoms which could not be explained by other diagnoses and thus defined the term long COVID - "a multisystem condition with a range of debilitating signs and symptoms which continue or develop after acute COVID-19 and persist for more than 4 weeks"(7). The most commonly mentioned signs and symptoms include shortness of breath, chronic cough, fatigue, malaise, myalgia, tingling sensations, memory and concentration impairment, olfactory loss, and many others (8-10). The mechanisms involved in the pathogenesis of long COVID are not fully understood, and numerous factors are thought to contribute. Firstly, it is thought that organ damage sustained in the acute phase of the disease plays an important role, and it can be found and radiologically ascertained even in mild cases (11, 12). The chronic reservoir of viruses in the body, as well as the disorders of immunological mechanisms, most commonly abnormal response of the T cells and reactivation of dormant viruses, are also often mentioned (13-15). The endothelial dysfunction, which is one of the most enquired mechanisms of thrombosis in acute disease, is sparsely mentioned in late COVID, although there are some studies suggesting microclots formation in various organ systems (16, 17). Kell and collaborators proposed that fibrinogen in the blood can undergo anomalous 'amyloid' transformation into a β-rich structure, resistant to proteolysis (fibrinolysis), forming fibrin amyloid microclots. In individuals with long COVID, platelet-poor plasma (PPP) exhibits extensive and persistent fibrin amyloid microclots, capable of entrapping proteins. These fibrin amyloid microclots may significantly contribute to the multifaceted symptoms of long COVID by obstructing capillaries, potentially explaining a range of observations, including breathlessness and thrombotic events such as acute myocardial infarction and stroke (18).

Literature search

Having in mind mechanisms of vascular complications in acute COVID infection and pathogenesis of long COVID, one would expect similar presentation and consequences of long COVID on human vasculature. In order to explore more information related to this particular topic, a wide search of the literature on the topic of "(long COVID* or DVT or arterial thrombosis or embolization*) and (long COVID or venous thrombosis* or

arterial thrombosis* or stroke or vascular complications*)" was conducted. Screening of titles and abstracts were performed initially and papers with potential inclusion of the data regarding long COVID and vascular symptoms or complications that occurred during the time span of more than then 4 weeks after COVID infection were explored in more detail. The authors included all types of publications since the data in the literature were scarce.

Discussion

Papers and research dealing with long COVID are mostly focused on symptoms and laboratory findings due to the nature of this condition. Data regarding vascular complications in these studies are either missing or the incidence of vascular complications was very low (19). Most useful papers showing a low prevalence of vascular complications in long COVID are already published in systematic reviews. Systematic review and meta-analyses showed that COVID-19 infection induces different manifestations in the convalescence phase: fatigue (1.72-fold), shortness of breath (2.60-fold), neurological symptoms, memory problems and concentration compared to an uninfected control group. The authors found a higher relative risk of symptoms in ICU patients and patients with severe infection compared to all hospitalized and non-severe infection patients. The severity of infection may have a significant impact on the likelihood of developing long COVID (20).

Another systematic review identified 55 conditions related to COVID infection manifesting after infection in the convalescent phase. Authors found that 80% (95% CI 65–92) of individuals with a confirmed COVID-19 diagnosis have various symptoms, signs, and changes in laboratory parameters (fatigue, anosmia, lung dysfunction, abnormal chest X-ray or CT scan, and neurological disorders). Most of the symptoms were similar to clinical presentation of COVID infection. Very few manifestations were related to the cardiovascular system and D-dimer was assessed in only two studies (150 patients), showing increased values in 30% of patients after COVID infection (21, 22). Risk of thrombosis in acute COVID infection has been reported, for both arterial and venous vasculature (23, 24). On the other side, the meaning of elevated D-dimer in the post-COVID time is still unclear. Mandal and collaborators showed elevated values in 30% of examined patients. It is important to know that patients who require ICU might be underrepresented in this particular study. As mentioned by the authors, a comparison of these results with other viral infections is not possible due to the lack of data. In the retrospective, observational, cross-sectional study in Sweden, on patients undergoing diagnostic tests for venous thromboembolism (VTE) in an integrated healthcare system covering a population of 465 000, increased risk for VTE in COVID-positive patients was proved (25).

A very important population includes patients with arterial or cardiovascular disease presenting before COVID infection. In this particular group, the risk of arterial and venous thrombotic events after COVID infection is substantially higher. Gianis and his team followed such a group of more than six hundred patients and found arterial thromboembolism in 27.3% (myocardial infarction, ischemic stroke, systemic embolism, major adverse limb event), venous thromboembolism in 6.9% (deep vein thrombosis, pulmonary embolism) and composite in 35.2% (26).

Based on clinical manifestations of long COVID syndrome, different types of this condition are proposed: the subtypes are non-severe COVID-19 multi-organ sequelae, pulmonary fibrosis sequelae, myalgic encephalomyelitis or chronic fatigue syndrome, postural orthostatic tachycardia syndrome, post-intensive care syndrome (PICS) and medical or clinical sequelae (MCS). Vascular manifestations are not included (27). On the other side, in one of the largest studies of the post-acute sequelae of COVID-19 that included 73 435 non-hospitalized patients and almost five million controls, as well as more than 13 000 hospitalized patients with seasonal influenza burden with coagulation disorders, pulmonary embolism, acute phlebitis, thrombophlebitis or thromboembolism were significantly higher. Hazard ratio for arterial thrombosis or embolisms was substantially lower. In a much smaller sample, Patel et al. found that the cumulative incidence of thrombosis (including arterial and venous events) at day 30 following discharge was 2.5% while the cumulative incidence of venous thromboembolism alone at day 30 post-discharge was 0.6% (28). An observational study done by Sjoland et al. which included 48 861 hospitalized and 894 121 non-hospitalized COVID-19 patients concluded that patients hospitalized for COVID-19 retained an elevated excess risk of VTE, mainly pulmonary embolism, even after 180 days, while the long-term risk of VTE in patients not requiring hospitalization was similar to that in the patients without COVID-19 (29). In another very detailed observational study, screening on D-dimer levels and venous complications showed very low rates in almost five hundred patients who were under prophylaxis (30). In patients with persistent respiratory symptoms after pneumonia, abnormal vascularization has been shown to be very frequent (31). Proximal arterial thrombosis has been shown in 5.4% of patients and perfusion abnormalities in 65.5% of patients. Summary of risk and incidence is presented in the **table 1**.

Focus of research in post-COVID syndrome and the incidence of cardiovascular symptoms is mostly related to arrhythmias, fatigue, and myocarditis (32). The evidence related to arterial or venous consequences is scarce. We are aware that endothelial activation in acute COVID-19 infection could be the reason for thromboembolic events in the arterial or venous system (2). There are rare clinical experiences that might cause suspicion that SARS-CoV-2 infection, a state of endothelial activation with downstream signaling pathways of low-grade inflammation and thrombosis may persist. The effect of COVID infection that induces immuno-thrombogenicity may persist longer than acute viral infection and induce a major thrombotic event, occurring even in individuals with weak or

Table 1. Summary of vascular complications in long COVID infection.

Vascular complications	Hazard ratio	Cumulative incidence
Patients with long COVID regardless clinical presentation and severity (27, 28)		
Coagulation disorders	14.31 (10.08–17.89)	
Arterial thrombosis	1.26 (0.69, 2.32)	
Venous thrombosis	3.05 (2.51–3.49)	0.6%
Pulmonary embolism	18.31 (15.83–20.25)	
Myocardial infarction		
Arterial and venous		2.5%
Patients with chronic cardiovascular diseases (26)		
Arterial thrombosis (ischemic stroke, myocardial infarction, embolism, major adverse limb event)		27.3%
Venous thromboembolism (deep vein thrombosis, pulmonary embolism		6.9%

moderate clinical presentation of COVID infection even after several weeks (32). Fan and collaborators reported severe thrombotic events in several previously healthy individuals, months after COVID infection. More importantly, COVID manifestations were mild or almost asymptomatic.

Conclusion

Based on the published literature, considering case reports, clinical studies, data from registries and systematic reviews available in the literature, vascular complications in the long COVID are very rare. Compared to a very high rate of thrombotic events in the acute COVID infection and their correlation with severity of clinical presentation of COVID infection, the role and presence of vascular complications in long COVID is without any significance. Future studies focusing on the pathophysiology of long COVID could probably reveal potential mechanisms and explanations for such a difference.

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