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REVIEW

Pulmonary Embolism in Post-CoviD-19 Patients, a Literature Review: Red Flag for Increased Awareness?

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Abstract
Although COVID-19 was primarily considered a respiratory illness, rapidly accumulating data suggest that COVID-19 is associated with a high incidence of venous thromboembolic complications.
The primary objective of this review article was to reveal whether we need to increase awareness of pulmonary embolism in the period following the COVID-19 infection given that the epidemiologic facts are still poor.
A literature search and a critical review of the collected studies were conducted. An electronic search of PubMed, Science Direct Scopus, Google Scholar, and Excerpta Medica Database (EMBASE) from June 2020 until June 2022.
The long-term health consequences of COVID-19 remain largely unclear. This review highlights the importance of awareness of the potentially increased incidence of venous thromboembolism in post-COVID-19 patients, even those with mild or asymptomatic disease. Further research is required to establish appropriate clinical management guidelines for the prevention of thromboembolic complications in the post-COVID-19 period.

Keywords Pulmonary embolism · Post–COVID-19 · Thromboembolic events

Introduction

Coronavirus disease (COVID-19) is an infection caused by the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1]. The clinical presentation of COVID-19 varies from mild to severe disease, provoking mild illness but also acute respiratory distress syndrome (ARDS), sepsis, as well as, multiorgan dysfunction[2]. Rapidly accumulating data suggest that COVID-19 is associated with coagulation abnormalities that increase the risk of both arterial and venous thromboembolic events (VTE)[3, 4]. The literature so far concerns studies that show an increased risk for thromboembolic events during COVID-19[5, 6]. In the literature, though, there are published data, mainly case reports that raise the red flag for a potentially increased risk of pulmonary embolism (PE) after COVID-19 infection[7]. This paper aims to discuss whether we need to increase awareness of post-COVID-19 PE. We will try to highlight the probability of PE after COVID-19 infection period.

Database Search Strategy

A critical literature review of the collected studies was conducted. An electronic search of PubMed, Science Direct Scopus, Google Scholar, and Excerpta Medica Database (EMBASE) from June 2020 until June 2022. A review of the titles and abstracts as well as a manual search of the reference lists were carried out.

Epidemiology

PE is a life-threatening manifestation of venous thromboembolism. Yearly, approximately 1 in 1000 persons suffers from PE worldwide[8, 9]. VTE is globally the third most frequent acute cardiovascular syndrome after myocardial infarction and stroke[10, 11]. COVID-19 is an ongoing

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global public threat. As of December 20, 2021, the numbers of confirmed cases and confirmed deaths reported to World Health Organization (WHO) were 273,900,334 confirmed cases and 5,351,812 deaths[12]. It also is clear that the prevalence of PE during the COVID-19 pandemic is increased[13–16].

Pathophysiology

Over the past 2 years, data extracted from studies concerning COVID-19, imply the strong correlation between SARS-COV-2 infection and induced coagulopathy. The unique coagulation pattern and the high incidence of VTE in patients with COVID-19 suggest that different mechanisms, beyond the already known, are involved in the COVID-19 Associated Coagulopathy (CAC).

The predisposition for thrombosis in COVID-19 is driven by at least two distinct, but interrelated, processes. The first one includes mainly large-vessel occlusion, usually due to thromboembolism. The second one, which is the predominant theory, concerns microvascular in situ immunothrombosis, as a consequence of innate immune system activation[17]. The model of immunothrombosis involves the interplay of many pathways, among them, viral-mediated endothelial dysfunction and immune system dysregulation, leading to platelet and leukocyte activation and aggregation. Additional pathways taking part in CAC are cytokine cascade and complement activation[6]. Each of these pathways, that contributes the immunothrombosis, plays a pivotal role in the composition of CAC pathogenesis. However, unspecified pathophysiological mechanisms may contribute to the occurrence of thromboembolic events in the post-infectious period.

The first step of SARS-CoV-2 infection happens when the virus enters lung alveolar epithelial cells by the interaction between the viral surface S (spike) protein and angiotensin-converting enzyme 2 (ACE-2) receptor through processes involving cell surface-associated trans-membrane protein serine 2 (TMPRSS2)[18]. Then, it conducted a process including, RNA translation and replication, as well as protein synthesis. SARS-CoV-2 buds in the endoplasmatic reticulum — Golgi intermediate compartment (ERGIC) or Golgi apparatus and exits the cell via a biosynthetic secretory pathway[19]. Research suggests that SARS-CoV-2 has the potential to leave cells as small secretory vesicles that then release the virus[20]. Barberis et al. identified the presence of SARS-CoV-2 RNA in extracellular vesicles (EVs), suggesting that the virus may spread the infection through the endocytic route[21]. EVs are lipid bilayer membrane-bound structures released from leukocytes, mainly monocytes, under physiological and pathological conditions. Their function is to transport active components (such as DNA, mRNA, microRNA, and proteins) to nearby or distant cells to help maintain their physiological state[22]. The SARS-CoV-2 RNA can be hidden, transported, released by EVs, and re-attack various tissues and organs through the circulatory system. EVs may play a "Trojan horse" role in viral RNA reappearance in recovered COVID-19 patients[23]. This theory can be one of the potential mechanisms for the COVID-19 complications in the post-infection period. In addition to their function as transporters, EVs play an important role in inflammation, coagulation, and immune regulation. The released virus from EVs can provoke direct endothelial injury, in addition to preexisting endothelial dysfunction during the infectious period. The ROADMAP-post-COVID-19 study documents that endothelial cell activation and hypercoagulability up to 62 days from symptom onset is a common alteration in COVID-19 survivors[24]. As a consequence, tissue factor (TF) releases from the medial layers of the endothelium, promoting the activation of the extrinsic coagulation cascade. The endothelial injury leads to platelet activation, adhesion, and aggregation. Activated platelets and endothelium secrete protein disulfide isomerase (PDI) which activates microvesicle-derived TF (type of EVs), resulting in the release of TF, accelerating further the coagulation process[6]. The damaged endothelial cells induce a membrane's molecule redistribution, leading to phosphatidylserine (PS) exposure in the outer cell membrane. PS is a membranous phospholipid normally sequestered in the inner leaflet of a cell membrane. PS exposure in the outer leaf of the cell membrane creates a catalytic surface for clotting factors which facilitate the conversion of prothrombin to thrombin[25]. Compared with patients without thrombosis, patients with thrombosis had significantly higher PS externalization[26]. Hence, the PS exposure due to viral infection may be another mechanism of coagulation activation[27]. The hypercoagulable state of COVID-19 is mainly due to a unique derangement in the hemostatic pathways. The presence of late thromboembolic events in the post-infectious period raises the scientists' interest, in discovering the possible pathophysiological mechanism. A potential explanation is given by the EVs, which can carry the virus to distant tissues and various organs including the vascular system, re-injuring the vascular endothelium in the convalescent phase of COVID-19 infection. The expression of TF and PS exposure on the EVs surface are also important factors in promoting coagulation disorders. Consequently, the SARS-CoV-2 persistence due to EVs may stimulate the endothelial cells, platelets, and other inflammatory cells promote the upregulation of procoagulant factors, and destroys the protective function of vascular endothelium, thereby causing abnormal coagulation[25]. These may be potential mechanisms that can explain the residual thrombotic risk in post-COVID-19 patients.

Discussion — Thromboembolic PE in Post-COVID-19 Patients

In the previous paragraph, we summarized the pathophysiologic events that could explain PE late in the course of the disease or even after the infectious period. Also, the effects of persistent viral replication, inflammation, hypoxia, and endothelial injury leading to thrombosis and organ dysfunction in the long COVID could also explain the late PE[28]. Reviewing the literature, though, only a few data from small studies or case reports support the increased risk of PE after COVID-19 infection. The initial reports pinpointing a high incidence of 27–30% [29, 30] of PE in patients with COVID-19 were followed by numerous data questioning the number mentioned above. We have also considered the difficulty of interpreting the high incidence of PE in critically ill patients that are by default a high-risk group[31]. A recent meta-analysis highlights the fact that the actual incidence of thromboembolic episodes during COVID-19 remains unclear, while at the same time the PE is more frequent in Intensive Care Unit (ICU) admitted patients[32]. Another study has revealed a total 2.5% incidence of both arterial and venous thrombosis at day 30 following discharge and venous thromboembolism alone at 0.6%[14]. A meta-analysis from Kings College Hospital in London[15] has revealed among others that the patients hospitalized with COVID-19 do not have higher risk for thromboembolic disease after discharge in comparison with the patients that are hospitalized due to other acute diseases. It seems that the information derived from the studies fluctuates considerably and at the same time there is a clear lack of homogeneity in the patient group selected and followed, although all studies share the common interest in exploring the incidence of VTE and the need for thromboprophylaxis. Two more small studies seem also to agree that the incidence rate of VTE in the first 30–42 days after hospitalization due to COVID-19 is 0.6–0.48% [33, 34]. A retrospective multicenter study on consecutive COVID-19 patients hospitalized at 7 Italian hospitals showed an association between late hospitalization and PE in COVID-19 that could possibly be explained by the longer bed rest, delayed anticoagulant prophylaxis administration as well as the pathophysiological mechanism involved in the later phases of COVID-19, characterized by the interplay between systemic hyper-inflammation state[35], immuno-mediated phenomenon and clotting system activation[36, 37]. In the same study, most PE were confirmed within 24 h after admission, suggesting that VTE was unrelated to hospitalization; probably, PE in COVID-19 is a progressive pathological process that begins in the early infection stage and manifests clinically in the late infectious phase leading to hospitalization later in the course of the disease[34]. The majority of the studies mentioned above refer to hospitalized patients that have been followed post-discharge from the hospital or are hospitalized. Not much is known though about the incidence of PE following a mild or uncomplicated or even asymptomatic COVID-19 infection. Our intention with this paper was to gather all the literature data including case reports in order to take a closer look at the patients, the course of their disease while COVID-19 positive and their presentation with VTE during post-COVID-19 period. Having said that, we wanted to show that even patients with mild COVID-19 infection might have increased risk for VTE after the infectious period. Data from case report studies describing PE in 52 patients at least 7 days after manifestation of COVID-19 infection were also taken into consideration. In Table 1, we summarize 52 reported cases, with an event of pulmonary embolism after COVID-19 infection. The minimum reported days after diagnosis is 7 days and the maximum is 180 days (mean 35.1 days) which agrees with the results of ROADMAP-post-COVID-19 study, documenting hypercoagulability up to 62 days[24]. The majority of the cases the time of clinical manifestation of PE is during the first month following the COVID-19 infection. In 40 cases out of 52, PE occurred in less than 36 days after infection. The majority of the patients were not under anticoagulation treatment mainly due to the fact that they manifest just mild disease during the infection. Namely, 32 cases didn't need hospitalization or were asymptomatic during COVID-19 infection. Two patients were under Low Molecular Weight Heparin (LMWH)[33] and one under oral anticoagulants[41]. The cases concern almost equally patients in the 4th, 5th, and 6th decade of life. Although a tendency can be described, with the case reports, we still need more research or/and registries in order to have a clear view about the incidence of PE after COVID-19 infection and the time period where there is an increased risk for PE. That could actually raise a valid question, weather we need to add COVID-19 infection as an extra risk factor during assessment of the probability for manifestation of PE.

Conclusion

We reviewed the literature trying to answer whether we should increase awareness of PE during the post-COVID-19 period, especially for patients with asymptomatic or mild disease during the infection. Though we already know that the incidence of VTE is highest during the first 19 days after hospital admission[72] unfortunately, the duration of VTE risk in non-hospitalized patients or with short hospital stays remains unclear[73]. Knowing that COVID-19 increases the probability for a patient to have an event of PE, we

Table 1 Summarized 52 reported cases, with an event of pulmonary embolism after COVID-19 infection

	Pts	G	Age yrs	Hospitalized during COVID-19 infection	Time between diagnosis of COVID19 and PE (days)
Bingwen Eug. Fan, 2021 [38]	1	M	39	No	76
Prakash Vaduluk, 2020 [39]	1	F	52	Yes	30
Abdoulaye Toure, 2020 [40]	1	F	26	Yes	94
Falmata L. Brem, 2021 [41]	2	M	66	Yes	23
		M	66	Yes	28
Timothy Pow, 2021 [42]	1	M	40	No	60
Abdulrahman Al H., 2020 [43]	2	F	50	No	20
		F	56	No	35
Franca Del Nonno, 2021 [44]	1	F	61	No	35
Muhanad Taha, 2021 [45]	1	M	41	No	152
Ayesha Jamil, 2021 [46]	1	F	47	No	180
Behshad N. Tabrizi, 2020 [47]	1	M	68	Yes	14
Falmata L. Brem, 2021 [48]	3	M	68	No	Not Known (Presence of IgG, IgM)
		M	60	No	Not Known (Presence of IgG, IgM)
		M	85	No	25
Phany B. I. Maloumbi, 2021 [59]	1	F	38	No	17
Emilia D'Elia, 2021 [49]	1	M	51	Yes	Not Known
J.C.Valencia M., 2021 [50]	1	F	52	Yes	28
Mohamad Kanso, 2020 [51]	2	M	68	Yes	15
		M	62	Yes	15
Sadaf Ali, 2020 [52]	1	F	52	Yes	25
Mana Rahimzadeh, 2020 [61]	1	M	61	Yes	36
Gagan Kaur, 2021 [53]	1	M	34	No	150
Andrew Baird, 2021 [54]	1	F	30	No	28
Hareton T. Vechi, 2020 [55]	5	M	63	No	23
		M	28	No	16
		M	34	No	27
		M	58	No	17
		M	55	No	17
Calin Pop, 2021 [56]	4	M	45	Yes	22
		M	42	Yes	18
		F	35	Yes	32
		M	25	Yes	16
Mats Beckman, 2020 [57]	1	M	51	No	49
Siri Overstad, 2020 [58]	2	M	39	No	27
		M	57	No	28
Mario Karolyi, 2020 [60]	4	M	45	No	21
		M	50	No	26
		M	45	No	18
		M	32	No	15
Mikkel Rodin Deutch, 2021 [62]	2	M	87	Yes	24
		M	61	Yes	9
De Pace D, 2021 [63]	1	M	72	No	90
Ruba M. Barnawi 2022 [64]	1	M	22	No	14
Saîda Amaqdouf, 2022 [65]	1	M	92	No	Unknown
Keerti Sitani, 2021 [66]	1	M	41	No	30
Takahashi Hidenori, 2022 [67]	1	F	83	Yes	16
Tomasz Czerski, 2022 [68]	1	M	49	No	20

Table 1 (continued)

	Pts	G	Age yrs	Hospitalized during COVID-19 infection	Time between diagnosis of COVID19 and PE (days)
Kok Hoe Chan, 2021 [69]	2	M	65	No	14
		F	85	Yes	7 (14 from symptoms)
Ersan Oflar, 2020 [70]	1	M	45	No	10
Maria Ioannou, 2022 [71]	1	M	44	Yes	27

anticipate that this will extend during the post-COVID-19 period[74]. There are only a few studies that managed to evaluate the incidence of VTE in post-Covid patients[33, 34]. Case reports data show that there is a wide range in the time frame between COVID-19 diagnosis and PE manifestation which need to be better understood. Additionally, it is still unclear whether PE following COVID-19 infection is a manifestation of the post-COVID-19 condition or not. The majority of case reports concerns patients that did not need hospitalization during the infection. It is necessary to define the critical time, following the resolution of COVID-19 during which patients are at high risk for developing PE. In conclusion, there is no hard evidence proving that a medical history of COVID-19 will increase the risk for PE but some indications that need to be further investigated. Further studies are needed to question a potential causal link between "post-COVID-19 PE" and preceding SARS-CoV-2 infection and to outline the high-risk period after the COVID-19 convalescence phase regardless of the severity of the infection.

Author contribution All authors contributed to the writing of this review.

Declarations

Ethics approval Fully compliant with ethical issues

Conflict of interest The authors declare no competing interests.

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