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Pulmonary embolism in patients with the Coronavirus Disease 2019

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ABSTRACT

Coronaviruses are RNA viruses causing infectious diseases. They had been responsible for 15% cases of a common cold before December 2019. With the new strain of coronavirus SARS CoV2 which causes COVID-19 disease, the ongoing pandemic surprised with the severity of symptoms and its course compared to the previously known mild respiratory tract infections. In the end of December 2021, over 274 million people were diagnosed with COVID-19 disease, and the total mortality amounted to nearly 5.4 million deaths in more than 200 countries. One of the potentially fatal complications of COVID-19 is pulmonary embolism (PE). It appears that PE has been associated with several coagulation abnormalities as well as with frequent significantly elevated concentration of D-dimer's. A higher D-dimer concentration in blood serum, in turn, has been associated with an increased risk of premature death. Moreover, inflammation, typical in the course of COVID-19, is considered a prothrombotic condition; higher interleukin 6 (Il-6) and C-reactive protein concentrations have been found in patients with more severe forms of COVID-19. So far, none specific for COVID-19 studies have been available with regard to the diagnosis and treatment of PE. Therefore, the practical approach is based on the experience of other groups of patients. Prevention of thrombotic events seems reasonable, at least in COVID-19 patients with the risk factors of developing venous thromboembolism. Low-molecular-weight heparins are most commonly prescribed (e.g. enoxaparin, dalteparin). Following the confirmed definite PE diagnosis, proper anticoagulation or, if necessary, thrombolytic treatment must be introduced.

Coronaviruses are RNA viruses causing infectious diseases in birds and mammals, including people [1]. However, infections caused by these viruses may be asymptomatic. It usually presents as mild symptoms similar to a common cold, although patients frequently end up developing severe complications which may lead to death [1–5].

For many years, four coronaviruses, HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63, have been present in human populations, and have been responsible for up to 15% of all cases of a common cold [6]. Three other coronaviruses identified in humans, i.e. MERS-CoV, SARS-CoV, and SARS CoV-2, account for more severe infections, i.e., the Middle East severe acute Respiratory Syndrome, Severe Acute Respiratory Syndrome, and the Coronavirus Disease 2019 (COVID-19), respectively [7, 8]. In the end of December 2021, over 274 million people were diagnosed with COVID-19, and the total mortality amounted to nearly 5.4 million deaths in more than 200 countries worldwide [9]. The beginning of the COVID-19 vaccination process in late 2020 provided the humanity with the expected efficient remedy. To date, although over 4400 million people globally have been vaccinated with at least one dose, it is still not enough to gain herd immunity [10].

The most common clinical symptoms of COVID-19 include fever, cough, fatigue, dyspnoea, accompanied with muscle pain, loss of smell and taste, diarrhoea, and weight loss [11–14]. Additionally, some patients also report nausea, emesis, and abdominal pain. The mean incubation time of the virus varies from 4.6 to 6.5 days [15]. It is crucial to bear in mind that the disease may progress to viral pneumonia, acute respiratory distress syndrome, multi-organ failure, and cytokine storm, which leads to death. Major exacerbation of the disease frequently occurs late, over two week following the infection [16]. Furthermore, COVID-19 affects various organs and systems. This, in turn, may lead to serious complications which are not as common or do not occur at all in case of infections caused by rhinoviruses, influenza viruses, adenoviruses, or older coronaviruses [12, 18].

Crucially, COVID-19 is associated with an increased risk of mortality. Among several serious consequences, pulmonary embolism constitutes one of the most common potentially life-threatening complications in COVID-19 patients [18–20], and the underlying causes are numerous. Similarly to other viral infections, COVID-19 is accompanied with an inflammatory response of varying severity, from mild to extreme. However, COVID-19 may be complicated by a cytokine storm along with several coagulation abnormalities, ranging from excessive bleeding to disseminated intravascular coagulation [21, 22].

In COVID-19, the coagulation is activated through several procoagulant mechanisms, including an increase in fibrinogen concentration, activation of platelets and complement pathway, as well as endothelial damage [23, 24, 26]. Interestingly, Han et al. noticed that D-dimer concentration is generally higher in COVID-19 patients than in the healthy individuals [25]. Individuals with a more severe COVID-19 course present higher D-dimer concentration than those with the mild forms [26–29]. Furthermore, other studies also indicate a positive correlation between the D-dimer concentration on admission, morbidity, and mortality rates [30, 31]. In fact, patients with higher D-dimer and fibrinogen-derived peptides concentrations, longer prothrombin time, and activated partial thromboplastin time were at an increased risk of death. Among those who died, a disseminated intravascular coagulation was found in 71.4% compared to 0.6% in the survivors. Several studies aimed to investigate the mechanisms and pathophysiology of the phenomenon referred to as COVID-19 associated coagulopathy (CAC). **Table 1** summarises the coagulation abnormalities found in COVID-19 patients.

Other causes for a higher prevalence of PE in COVID-19 patients include inflammation, immobilization, the coexistence of prothrombotic diseases, and pharmacological therapy. It is crucial to bear in mind that inflammation is considered a prothrombotic condition. Thus, higher concentrations of interleukin 6 (Il-6) and C-reactive protein are typical in COVID-19 patients [28]. Additionally, critically ill patients frequently develop sepsis and septic shock, both of which may lead to a disseminated intravascular coagulation [23], whereas common respiratory and urinary tract infections also temporarily increase the risk of PE [32].

Individuals with symptomatic COVID-19 show poorer exercise tolerance due to fatigue as well as dyspnoea, and they are hospitalized or subject to quarantine. Consequently, patients are either

Table 1. Changes in blood coagulation parameters in COVID-19 patients [25–28]

Changes in blood coagulation	COVID-19 patients vs. healthy individuals
APTT	Longer
PT	Longer
D-Dimer concentration	Higher
INR	Higher
FDP concentration	Higher
Fibrinogen concentration	Higher
Anti-Thrombin III concentration	Lower

Abbreviations: APTT – activated partial thromboplastin time, FDP – Fibrin degradation products, INR – International normalized ratio, PT – prothrombin time.

immobilized, or have a dramatically limited physical activity, which in itself is associated with an increased risk of thromboembolism. Moreover, numerous patients with a more severe COVID-19 course report other prothrombotic comorbidities, such as obesity, smoking, diabetes [33], advanced age, cancer, or prostate hypertrophy in men. Another risk factor for thromboembolism is a prolonged fever which is frequently accompanied by dehydration, as well as the fact that COVID-19 patients with a more advanced respiratory tract involvement require steroid treatment which also has a prothrombotic effect.

Increased numbers of deep vein thrombosis and life-threatening PE have been observed in COVID-19 patients (**Table 2**). Poissy et al. reported a surprisingly high PE number in 107 patients at the Intensive Care Units in Lille University Hospital in France [34], where in comparison with the pre-COVID19 period, the rate of PE was two-fold higher. Furthermore, PE prevalence was twice as high in COVID-19 patients than in individuals presenting with influenza, who were admitted to the same unit in 2019, whereas PE symptoms usually developed during the 6th day of the Intensive Care Unit hospitalization [34]. Grillet et al. [35] diagnosed acute PE in 23 out of 100 COVID-19 patients who presented with severe clinical signs and symptoms, such as an increased respiratory rate, decreased blood oxygen saturation, temperature > 40°C, the presence of other comorbidities, and a need of mechanical ventilation. According to their study, PE was diagnosed within the first 12 days of the onset of symptomatic COVID-19 infection. In fact, observations from other countries confirmed these findings, e.g. Poyiadji et al. [36] have shown that 72 out of 328 patients diagnosed with COVID-19 also developed PE. Nevertheless, most patients from this study did not require admission to the Intensive Care Unit.

The diagnosis of PE in COVID-19 patients constitutes a challenge, since most clinical signs and symptoms are non-specific for acute PE. A number of the clinical findings present in PE are also frequently found in COVID-19 patients who do not develop PE, i.e. both COVID-19 and PE patients complain of dyspnoea, reduced exercise tolerance, tiredness, and some with chest pain and reduced blood oxygen saturation. Additionally, the D-dimer concentration is increased in both COVID-19 and PE patients. Therefore, the principles or prognostic scores usually applied for the

Table 2. Overview of the studies regarding pulmonary embolism prevalence in COVID-19

	Country	Number of patients	Diagnosed PE	% of PE
Poissy et al. [34]	France	107	22	20.6
Grillet et al. [35]	France	100	23	23
Poyiadji et al. [36]	USA	328	72	21.9
Helms et al. [37]	France	150	25	16.7
Lodigiani et al. [38]	Italy	61	2	3.6
Klok et al. [39]	Denmark	184	65	35
Thomas et al. [40]	Great Britain	63	5	7.9
Middeldorp et al. [41]	The Netherlands	198	11	5.6

Abbreviations: PE – pulmonary embolism.

diagnosis of PE should also be used in COVID-19 patients, and up to date, no distinct or better approaches have been proposed. **Table 3** includes the prognostic scale for PE, and **Tables 4** and **5** summarises the two scores for PE prediction.

On the basis of the available literature and the analysis of three different COVID-19 patients from our centres, we have summarised the values of the Wells' score, the Revised Geneva Score, as well as PESI, and sPESI scores.

It is noteworthy that according to the Wells' score, 7 out of 12 COVID 19 patients with confirmed PE presented a low probability of PE (**Table 6**). In contrast, according to the Geneva Score, 5 of these patients should be categorized as belonging to the low PE probability group. Moreover, neither of the scales classified any of the patients as a high probability of PE. However, prior observations suggest that prognostic scales for PE are not sensitive and specific enough

Table 3. The Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) prognostic score for pulmonary embolism

	PESI	sPESI
Age	Age in years	1 (if >80)
Sex	Male (10)	-
Neoplasm present or not	30	1
Heart failure	10	1
COPD	10	1
Heart Rate >110/min	20	1
Respiratory Rate >30/min	20	-
Systolic Blood Pressure <100	30	1
Temperature <36	20	-
Confusion	60	-
Blood oxygen saturation <90%	20	1

Scoring: (risk)	PESI	sPESI
Very low <65	0–1.6%	0–1.0% risk of death
Low 66–85	1.7–3.5%	>1–10.9% risk of death
Moderate 86–105	3.2–7.1%	
High 106–125	4–11.4%	
Markedly high >125	10–24.5%	

Abbreviations: COPD – chronic obstructive pulmonary disease

Table 4. The Wells' score for the prediction of pulmonary embolism

	Wells (Original)	Wells (Simple)
Previous PE or DVT	1.5	1
Immobilisation for at least three days, or a surgery in the four previous weeks	1.5	1
Malignancy	1	1
Haemoptysis	1	1
Heart Rate > 100 beats/min	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1

Interpretation (Original Scale):	
>6 points	High probability
2–6 points	Moderate probability
<2 points	Low probability
Interpretation (Simple):	
≥2 points	Probably PE
<2 points	PE unlikely

Abbreviations: DVT – deep vein thrombosis; PE - pulmonary embolism.

Table 5. The Revised Geneva Score for the pre-test probability of pulmonary embolism

Revised Geneva Score	Points
Previous PE or DVT	3
Surgery (under general anaesthesia) or the lower limb fracture in the past month	2
Malignancy	2
Haemoptysis	2
Age >65	1
Unilateral lower limb pain	3
Pain on deep palpation of the lower limb and unilateral oedema	4
Heart Rate 75–94 beats/min	3
>95	5

Interpretation:	
0–3 points	Low probability
4–10 points	Moderate probability
11 and more points	High probability

Abbreviations: DVT – deep vein thrombosis; PE – pulmonary embolism.

Table 6. Pulmonary embolisms in COVID-19 patients – collected cases and our data

Country	Gender	Age	Comorbidities	Wells scale	Geneva scale (revised)	sPESI	PESI
Abington, USA [42]	F	59	Hypertension, diabetes	1.5	5	2	99
London, UK [43]	M	53	none	1	5	0	63
San Diego, USA [44]	M	42	none	1	2	0	72
Lugano, Switzerland [45]	M	50	chronic kidney disease, hypertension, hepatitis B	2	5	1	80
Manchester, UK [46]	M	52	none	1	0	1	62
Birmingham, UK [47]	F	52	Obesity, diabetes	2	5	3	202
Istanbul, Turkey [48]	F	41	Diabetes	1	0	3	161
New York, USA [49]	M	38	Obesity	2	5	2	118
Poznan, Poland	F	39	Hypertension	3	5	0	39
Florence, Italy	M	64	Previous myocardial infarction, allergic asthma	1.5	3	0	74
Wroclaw, Poland	F	69	None	1	0	0	89
London, UK	M	48	Obesity	2	5	2	118

[50]. The abovementioned data indicate that the active COVID-19 should probably be included in the modified Wells' scale and Geneva Score in order to improve their applicability in this particular group of patients. Therefore, to achieve this a large multicentre registry of patients with COVID-19 who developed PE and who did not develop PE should she established.

Although there are several different PE diagnosis modalities, in COVID-19 patients probably the most frequently applied method is computed tomographic pulmonary angiography. According to Sabri et al. [51], chest CT shows ground-glass opacities and consolidations in most COVID-19 patients (93.4% and 92.6%, respectively). In addition, nearly two-thirds (63.5%) of patients presented the peripheral distribution of lung abnormalities and some central and diffuse opacities (14.3% and 17.5%, respectively). In fact, compared with the reverse-transcription polymerase chain reaction (RT-PCR), chest CT may constitute a more reliable, practical, and faster method to diagnose and assess COVID-19, particularly in the area affected by the epidemic. As Ai, Yang et al. observed, with RT-PCR results as the reference standard in 1014 patients, the sensitivity, specificity, and accuracy of chest CT in indicating COVID-19 infection were 97%, 25% and 68%, respectively [52]. In some centres, lung ultrasound is also employed, particularly at the Emergency Departments or in cases of patients in a critical condition. Moreover, lung point-of-care ultrasound (POCUS) has shown sensitivity and specificity similar to chest CT when diagnosing interstitial pneumonia, which is also an effective method in terms of the visualization of the sub-pleural lung infarctions typical of pulmonary embolism.

It is vital to bear in mind that echocardiography plays an essential role in diagnosing and monitoring patients with suspected PE [53]. In fact, it may directly visualize the thrombus or thrombi within the right ventricle, particularly in patients with the prothrombotic state, such as SARS-COV-2. Echo allows visualizing right ventricular dilatation and dysfunction. It also allows assessing pulmonary artery pressure and elevated pressure features in the form of interventricular septal flattening. The critical part of the echo is the McConnell's sign, characterized by akinesia of mid-segment of RV free wall with a normal apex motion [54]. Although echocardiography may have a low sensitivity in diagnosing PE, at the same time it shows high accuracy in diagnosing a large PE [55]. An essential element, therefore, is thrombotic events prevention which should be introduced to COVID-19 patients with risk factors of developing venous thromboembolism to prevent PE development [56]. Nevertheless, a recent systematic review has pointed out other risk factors of developing directly PE in covid-19 patients [57], such as mechanical ventilation status or parenchymal damage. Interestingly, authors of this study claim that age and typical comorbidities were nor associated with the occurrence of PE.

The most commonly prescribed medications include low-molecular-weight heparins (e.g. enoxaparin, dalteparin), as well as alterna-

tive pharmacological therapies. [58, 59] However, one retrospective study indicated that the use of fondaparinux, instead of low-molecular-weight heparins, should be discouraged [60]. Yet, there is limited evidence that Oral Anticoagulants are ineffective in reducing mortality [61], and apixaban and rivaroxaban concentrations may be increased during the treatment with sarilumab or tocilizumab [56]. Once the definite PE diagnosis is confirmed, an anticoagulation treatment should be initiated, which usually comprises low-molecular-weight heparin or unfractionated heparin [58]. In PE patients who are hemodynamically unstable due to severe and unresponsive hypotonia and/or shock, thrombolysis is recommended with a recombinant fibrin-specific plasminogen activator. Therefore, it is still uncertain which therapy should be eventually chosen for patients with arteriovenous thromboembolism, including those with PE, and further investigations are necessary. Similar considerations apply to the prevention of embolism incidents. Despite these concerns, treatment based on the current guidelines should be introduced in clinical practice and such guidelines have been developed in several countries [58].

Summarizing, COVID-19 infection is associated with multiple coagulation abnormalities leading to the development of PE, particularly in the critically ill patients. PE constitutes one of the most serious complications accompanying COVID-19, as it substantially increases mortality. Hence, the diagnostic approach and the applied therapy should be the same as in non-COVID-19 patients. So far, no specific studies with regard to the diagnosis and treatment of PE in COVID-19 patients have been available. Therefore, it appears that this clinical challenge requires more attention and deserves a prospective clinical evaluation.

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The authors declare no conflict of interest.

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