VIA MEDICA

EDITORIAL COMMENT

Cardiology Journal
2020, Vol. 27, No. 5, 481–484
DOI: 10.5603/CJ.2020.0153

ISSN 1897–5593

COVID-19 and its implication for venous thromboembolism

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Coronavirus disease (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is responsible for the ongoing 2019–2020 pandemic. Infected patients can be asymptomatic or show a range of symptoms including: fever, cough, fatigue, and dyspnea. These symptoms, except fever, are also typical for acute pulmonary embolism (APE). The overlapping symptoms of this diseases may result in under-recognition of APE.

Patients with COVID-19 infections are at an increased risk of thromboembolic complications. In hospitalized patients, a sudden deterioration of crucial vital parameters including tachycardia, hypotension, desaturation should suggest APE. Of note, temporary SIQIIITIII pattern in electrocardiogram, similar to alterations observed in APE was reported in COVID-19 patients [1].

Incidence of venous thromboembolism in patients with COVID-19

There is an increasing number of reports on thromboembolic complications in COVID-19 patients. Klok et al. [2] analyzed data of 184 patients (mean age 64 ± 12 years, 24% female) admitted to the intensive care unit (ICU) of Dutch hospitals due to proven COVID-19 pneumonia. All patients received at least prophylactic doses of nadroparin. The composite outcome was symptomatic APE, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism. The cumulative incidence of the composite outcome was 31% (95% confidence interval [CI] 20–41%), of which computed tomography pulmonary angiogram and/or ultrasonography confirmed venous thromboembolism (VTE) in 27% (95% CI 17–37%) and arterial thrombotic events in 3.7% (95% CI 0–8.2%). APE was the most frequent thrombotic complication (n = 25, 81%) [2].

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Received: 12.06.2020 Accepted: 26.08.2020

Interesting data come from Wuhan, China, published by Cui et al. [3], 81 patients (mean age 59.9 ± 14.1 years, 54% female) with severe coronavirus pneumonia were enrolled. The incidence of VTE in these patients was 25% (20/81), of which 8 patients with VTE events died [3]. Wichmann et al. [4] performed complete autopsies of the 12 consecutive COVID-19 positive deaths. Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom VTE was not suspected before death. APE was the direct cause of death in 4 patients [4].

In a recently published, prospective study, Helms et al. [5] described the COVID-19 induced thrombotic complications in 150 consecutive COVID-19 acute respiratory distress syndrome patients. Despite anticoagulation 64 clinically relevant thrombotic complications were mainly diagnosed as APE (16.7%) [5].

There is also interesting data from Lombardy, an Italian region that was most affected by the pandemic. In one paper, all cases of COVID-19 in-hospital patients undergoing duplex ultrasound for clinically suspected deep vein thrombosis. Of 101 duplex ultrasounds performed, 42 were positive for deep vein thrombosis. Moreover, in 24 patients APE was diagnosed. Three patients in ICU were already under anticoagulant therapy, while the rest were receiving prophylactic dosages of low molecular weight heparins [6].

The available data support the high incidence of thromboembolic complications in COVID-19 patients despite thromboembolism prophylaxis.

Potential mechanisms of increased VTE risk in COVID-19 patients

Several mechanisms in patients with COVID-19 potentially promote the development of VTE. They fulfil at least two of the three criteria of Virchow's triad: reduced venous flow from immobility, as well as prothrombotic changes due to inflammatory state [7]. Vessel wall changes, the third criteria of Virchow's triad, may also be present in infected patients Moreover, hypoxia in COVID-19 pneumonia subjects may also be a factor for increasing the risk of thromboembolic complications.

Serum level of angiotensin 2 is significantly elevated in infected patients, activating the renin––angiotensin system, which can cause widespread endothelial dysfunction. It is worth noting that the virus can bind to the endothelial cells via angiotensin 2 receptors — which are present mainly in the lungs, heart, and kidneys, followed by endothelial cells. This process may finally damage blood vessels and increase the risk of thrombosis [8]. It is also possible that antiphospholipid antibodies, that appear transiently in critically ill patients, may cause an increased risk of thromboembolism. There is a case report of 3 critically ill patients with confirmed COVID-19. They presented clinically significant ischemia of the lower limbs and multiple cerebral infarcts. Among these patients, antiphospholipid antibodies were detected [9].

Laboratory findings and diagnostic approach in patients with COVID-19

In COVID-19 patients the most typical laboratory findings include leukopenia, lymphocytopenia, mild thrombocytopenia, prolonged prothrombin time, increased D-dimer levels, and high fibrinogen level at the beginning of the disease followed by low fibrinogen levels in severe cases [4, 10, 11]. Increased values of D-dimer may be secondary to an infection and inflammation. Therefore, in COVID-19 patients, the specificity of D-dimer tests in diagnostics of VTE is lesser than in a healthy population. Disseminated intravascular coagulopathy is present in severe cases of SARS-CoV-2. It is recommended only to order diagnostic tests for pulmonary embolism when it is clinically suspected, however pulmonary embolism should be considered in differential diagnosis. Even if the specificity of D-dimer tests may be lower, it is still worthwhile following diagnostic algorithms starting with pre-test probability and D-dimer testing. This may reduce the number of necessary computed tomography-scan examinations with associated complications, as well as the associated deployment of resources and personnel for transporting a patient for a computed tomography scan with isolation precautions. Multidetector computed tomographic pulmonary angiography is the method of choice for imaging pulmonary vasculature in patients with suspected APE. In hemodynamically unstable patients, transthoracic echocardiography may be a first line examination. Right ventricular overload and dysfunction might be sufficient to prompt immediate reperfusion without further testing [12].

Lower limb compression ultrasonography may be useful in COVID-19 patients. Compression ultrasonography has a sensitivity > 90% and specificity > 95% for proximal symptomatic deep vein thrombosis. Compression ultrasonography should be a part of point of care ultrasound particularly in patients with unexplained right ventricular dysfunction, unexplained hypoxemia or in patients

with suspected APE who are unable undergo further evaluation.

Every single physical examination, laboratory test, or imaging of the patients including computed tomographic pulmonary angiography, compression ultrasonography, and echocardiography, requires the full protection of staff. Additionally, all equipment should be sterilized.

According to the literature, an increase of D-dimer level correlates with an increase in hospital mortality. Tang et al. [11] revealed data of 183 consecutive patients with confirmed coronavirus pneumonia. The overall mortality was 11.5%. The non-survivors revealed significantly higher D-dimer levels compared to survivors (2.12 [0.77–5.27] vs. 0.61 [0.35–1.29] μg/mL, $p < 0.001$) [11].

Recently, Figliozzi et al. [13] published a metanalysis included 49 studies and a total of 20,211 patients. An increased D-dimer level was related to adverse combined outcome (death, severe presentation, hospitalization in ICU and/or mechanical ventilation (odds ratio [OR] 4.39, 1.85–10.41, $p = 0.003$) and death (OR 4.40, 1.10–17.58, $p = 0.04$) [13].

Treatment of VTE patients

According to the European Society of Cardiology (ESC) guidelines, initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of APE, while diagnostic workup is in process [12]. It is very important in COVID-19 patients among whom most have a high or intermediate clinical probability of VTE. Treatment of VTE should be conducted in accordance with the ESC guidelines on the basis of risk assessment. Hemodynamically unstable, high-risk patients, should undergo immediate reperfusion by thrombolysis. It should be noted that many of the patients with COVID-19 have an absolute or a relative contraindication to thrombolysis such as thrombocytopenia, disseminated intravascular coagulation or a recent invasive procedure. Percutaneous catheter direct treatment should be considered for patients with high-risk APE, in whom thrombolysis is contraindicated or failed or for intermediate high risk with hemodynamic deterioration on anticoagulation treatment [8].

The anticoagulation therapy for stable APE patients is usually low molecular weight heparin (LMWH) or direct oral anticoagulants (DOAC). Unfractionated heparin may be initially preferred in intermediate-high risk patients and in subjects with severe renal failure or extreme obesity. After initial heparin treatment in stable APE patients, DOAC is preferred. However, drug interactions between DOAC and medical treatment of COVID-19 should be considered. Lopinavir/ritonavir inhibit cytochrome P450 3A4 and thus may increase the activity of NOAC — and therefore, the risk of bleeding. It should be emphasized that vitamin K antagonists are not recommended, except for patients with mechanical valves or antiphospholipid syndrome [14].

Thromboprophylaxis

Due to the increased risk of thromboembolic complications in patients with COVID-19, International Society on Thrombosis and Hemostasis (ISTH) and American Society of Hematology (ASH) guidelines advise prophylactic LMWH in all hospitalized COVID-19 patients in the absence of any contraindications [15, 16]. Therefore, thromboprophylaxis should be considered in all hospitalized patients due to COVID-19. Some authors recommended considering higher prophylactic doses of anticoagulation such as enoxaparin 0.5 mg/kg b.i.d. or 1 mg/kg once daily [2, 7]. Similar, according to CHEST Guideline and Expert Panel Report all hospitalized patients with COVID-19 are at increased risk of VTE. Therefore experts suggest against individualized VTE risk assessment and suggest anticoagulant thromboprophylaxis in all hospitalized patients with COVID-19 in the absence of contraindication [17]. Only a few papers address the issue of extended duration prophylaxis. Post discharge VTE and major bleeding rates in COVID-19 patients are currently unknown. Most experts recommended against routine extended, post discharge, duration prophylaxis in hospitalized patients, although an individualized approach for each patient should be considered [17].

Conclusions

Patients with COVID-19 infections are at increased risk of thromboembolic complications, a potentially preventable cause of death. Hospitalized patients should receive VTE prophylaxis. The diagnostic approach should be carried out according to the ESC guidelines, but physicians must be aware of the lower specificity of the D-dimer test. Every single physical examination, laboratory test, and imaging requires the full protection of staff. The anticoagulation therapy for stable VTE patients is usually LMWH or DOAC; vitamin K antagonists are **not recommended**.

Conflict of interest: None declared

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