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Review

How to screen and diagnose Deep Venous Thrombosis (DVT) in patients hospitalized for or suspected of COVID-19 infection, outside the intensive care Units

Short Title : Deep Vein Thrombosis screening in COVID-19 patients

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Summary

Introduction. The Coronavirus disease-2019 outbreak (COVID-19) has been declared a pandemic by the World Health Organization. Studies report both a severe inflammatory syndrome and a procoagulant state in severe COVID-19 cases, with an increase of venous thromboembolism, including pulmonary embolism (PE) and deep vein thrombosis (DVT). In this context, we discuss the use of doppler ultrasonography (DUS) in the screening and diagnosis of DVT in ambulatory and hospitalized patients with, or suspected of having, COVID-19, outside the intensive care unit (ICU).

Material and Methods. Non-systematic review of the literature.

Results. In patients hospitalized for or suspected of COVID-19 infection with the presence of either a) DVT clinical symptoms, b) a strong DVT clinical probability (Wells score > 2) or c) elevated D-dimer levels without DVT clinical symptoms and without PE on lung CT angiogram, DVT should be investigated with DUS. In the presence of PE diagnosed clinically and/or radiologically, additional systematic DVT screening using DUS is not recommended during the COVID-19 pandemic. The use of 4-points compression DUS for DVT screen and diagnosis is the most appropriate method in this context.

Discussion. Systematic DUS for DVT screening in asymptomatic COVID patients is not recommended unless the patient is in the ICU. This would increase the risk of unnecessarily exposing medical staff to SARS-CoV-2 and monopolizing limited resources during this period.

Keywords: venous thromboembolism, pulmonary embolism, COVID-19 associated coagulopathy, COVID-19 pandemic, Four-points Compression Ultrasound, Doppler Ultrasound, Wells score.

Introduction

An outbreak of viral pneumonia of unknown etiology was first reported in December 2019 in the city of Wuhan, China. This disease, now called COVID-19 (COroNaVirus Disease-2019), is caused by a viral infection from the coronavirus family, SARS-Cov-2.¹ By March 2020, this epidemic had spread to almost every country in the world and was declared a pandemic by the World Health Organization (WHO).² SARS-Cov-2 is an RNA virus that has acquired the ability

to infect humans. The virus can penetrate cells via certain receptors, such as the Angiotensin Converting Enzyme 2 (ACE2) receptor,³ which is expressed on pulmonary alveolar cells, cardiomyocytes, and endothelial cells.³⁻⁵ It has a high level of transmissibility, with an R0 (basic reproductive number) that ranges between 2.2 and 5.7, compared to 1.3 for seasonal influenza.⁶ COVID-19 is associated with a high mortality rate, ranging from 4.3% to 30% in the published literature.^{3,7-11} Elderly patients who either have comorbidities (obesity, managed hypertension, diabetes), or who are admitted to intensive care (21.9% mortality in patients over 80 years old),^{11,12} are at particularly high risk of life-threatening complications.

Recent studies report both a severe inflammatory syndrome and a procoagulant state (*i.e.* COVID-19 associated Coagulopathy) in severe COVID-19 cases,^{5,11,13-16} with a significant increase in the incidence of venous thromboembolism (VTE), including both pulmonary embolism (PE) and possibly deep vein thrombosis (DVT).^{5,11,14,15,17-21} In this context, the Saint-Louis hospital (APHP, Paris) pneumology and infectious disease teams, who are on the front-line treating COVID-19 patients, have called for a local hospital consensus on the use of doppler ultrasonography (DUS) and the role of vascular disease specialists in the screening and diagnosis of DVT in ambulatory and hospitalized patients outside the intensive care Unit, with or suspected of having a COVID-19 infection.

I – Increased incidence of VTE

With the pandemic spread of SARS-Cov-2 infection, several studies began to report a high incidence of VTE in patients hospitalized for COVID-19, particularly in intensive care units.^{20,22} In response to this, a subset of centers across different countries began to systematically perform computed tomography (CT) imaging in every patient hospitalized with COVID-19, to simultaneously confirm a diagnosis of SARS-Cov-2 pneumonia and to screen for PE (Figure 1).²³ It has therefore been possible, with progression of the pandemic, to collect data on the incidence of PE in COVID-19. The main incidence data to date are summarized in Table 1.²⁴

In a first retrospective study¹⁷ of 1008 patients hospitalized in Wuhan for COVID-19, 10 of 25 (40%) patients who received a chest CT were diagnosed with a PE. A second Chinese study²⁵ of 81 patients treated in intensive care for COVID-19 who were not treated with pharmacological thromboprophylaxis, identified DVTs in 25% of patients (n = 20/81, including n = 8 deaths [10%]). Finally, in March 2020, a published Italian clinical case study²⁶ reported how a patient hospitalized for SARS-Cov-2 pneumonia and treated with lopinavir / ritonavir and

hydroxychloroquine presented with a massive bilateral proximal PE on CT scan without associated DVT.

Several French studies have since reported similar rates of VTE in COVID-19 hospitalized patients. One retrospective single-center study (CHU Besançon)¹⁹ found that 23% of patients hospitalized for a severe form of COVID-19 were diagnosed with a PE (n = 23, 95% CI, 15%-33%). In this study, a PE diagnosis was identified as a severity factor, with 74% (n = 17 of 23) of COVID-19 patients with PE treated in intensive care compared to 29% (n = 22, p <0.001) of COVID-19 patients without a PE. Similarly, 65% (n = 15 of 23) of COVID-19 patients with a PE required mechanical ventilation compared to 25% of patients without a PE (n = 19, p <0.001). Comparable results were presented in a French two-center retrospective study (CHU Strasbourg)²⁰ of 106 COVID-19 patients, which reported a 30% PE rate on chest CT scan (n = 32/106, 95%CI, 22%-40%).

A prospective multicenter study (Strasbourg, France) reported 64 thrombotic events (arterial and venous combined) in 150 COVID-19 patients treated in intensive care unit.²¹ Twenty-five of these events were PEs (16.7% incidence rate), which were detected on average 5.5 days after admission. A comparison of 77 COVID-19 patients and 145 non-COVID patients with acute respiratory distress syndrome was performed by propensity score matching. In comparison with the cohort of 145 patients hospitalized in intensive care for non-COVID-19 acute respiratory distress syndrome, the incidence of PE was significantly higher in the COVID-19 group (n = 9 or 11.7% vs n = 3 or 2.1%; OR 6.2 (95%CI, 1.6-23.4); p = 0.008). A second French study (Lille, France) found a 20.6% rate of VTE in COVID-19 intensive care patients, which is significantly higher (versus 6.1%) than for the same period a year earlier in 2019 (control cohort, excluding COVID-19).²⁷ Additional studies further confirmed these data for patients hospitalized in intensive care units and when one of us performed routine duplex ultrasound examination of the lower limb veins systematically in 56 intubated and mechanically ventilated patients with SARS-CoV-2 pneumonia a prevalence as high as 45% VTE was found.²⁸

Studies are showing, however, that VTE incidence rates remain high when COVID-19 patients are administered standard prophylactic doses of anticoagulants. A Dutch retrospective study^{18,29} of 184 COVID-19 patients systematically treated with standard prophylactic doses of LMWH reported on the incidence rate of a composite VTE outcome measure that included 1) symptomatic acute PE, 2) DVT, 3) ischemic stroke, 4) myocardial infarction and/or systemic

arterial embolism. The cumulative incidence rate, adjusted for competing risk of death, was 49% (95% CI, 41% - 57%), over a median of 14 days. Most thrombotic events were PEs (87%, 65/75), and the mortality rate was 22% (n = 41 of 184). Recently Middeldorp et al³⁰ reported an increased incidence of DVT in COVID-19 patients in intensive care (ICU) (59%, 95% CI, 42-72) compared to patients not in ICU (9.2%, 95%CI, 2.6-21) after 21 days of follow-up and despite standard thromboprophylaxis.

II – COVID-19-associated coagulopathy (CAC)

Several factors have been associated with the occurrence of thrombotic complications in severe forms of COVID-19.^{3,13,14,31-33} This is in addition to established individual risk factors for thrombosis (ie.: age, obesity, inherited or acquired thrombophilia, active cancer, pregnancy, postpartum) and risk factors associated with hospitalization (immobilization > 3 days, surgery < 1 month, mechanical ventilation, catheter). COVID-19-associated coagulopathy (CAC) is predominantly associated with:

- The systemic inflammatory response and overproduction of cytokines ("cytokine storm") induced by viral infection,^{16,34} which results in an imbalance between procoagulants and anticoagulants and subsequent thrombin generation (thrombo-inflammation).^{34,35}
- Microvascular thromboses (microthrombi), which have been identified in pulmonary, cardiac, and renal vascular beds at autopsy in patients who died from COVID-19,^{36,37} suggesting their involvement in multi-organ failure often observed in severe forms of COVID-19.¹³ The presence of thromboses, both venous and arterial, as well as endothelial and epithelial necrosis, points to a state of systemic as well as localized hypercoagulability.
- Activation of endothelial cells, which could contribute to the procoagulant state in COVID-19 patients with severe forms of the disease.^{13,38,39}
- Tissue hypoxia, which is observed in severe forms of COVID 19, could increase the thrombotic risk by stimulating the transcription of factors such as the fibrinolysis inhibitors Plasminogen Activator Inhibitor 1 (PAI-1) and Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), thereby leading to a fibrinolytic shutdown.⁴⁰
- Blood stasis (Virchow's triad,⁴¹) in these critically ill, bedridden, and immobilized patients, especially in intensive care, is also a major risk factor for VTE.

- Advanced age and obesity have been identified as individual risk factors for mortality in COVID-19,^{3,42} which are also well-established VTE risk factors.⁴¹

D-dimers are produced during the degradation of fibrin by the fibrinolytic system, which is activated when a thrombus is formed.⁴³ It is an early marker of thrombosis because fibrinolysis is triggered within minutes of the onset of clot formation.^{44,45} Therefore, D-dimer blood level monitoring in patients hospitalized for or suspected of COVID-19 infection, within or outside intensive care Units, is being studied as a potential marker of VTE, although their threshold levels still have to be determined in this clinical setting. A first retrospective study¹⁵ of 183 patients with a diagnosis of COVID-19 who were treated with antiretrovirals and supportive care reported statistically significant elevated levels of D-dimer (2.12 µg/mL, CI = 0.77-5.27 versus 0.61 µg/mL, CI = 0.35-1.29, $p < 0.001$) and fibrin degradation product (7.6 µg/mL, CI = 4.0-23.4 versus 4.0 µg/mL, CI = 4.0-4.3, $p < 0.001$) on admission, between non-survivors ($n = 21$) and survivors ($n = 162$). Prothrombin time was also increased on admission in patients who later died of the disease compared to survivors (15.5 sec, 95% CI, 14.4 - 16.3, versus 13.6 sec, 95% CI, 13.6, 13.0-14.3, $p < 0.001$). Two other studies in patients with COVID-19 have reported that mean D-dimer levels are significantly higher in patients with PE than in patients without PE (respectively 6.110 +/- 4.905 µg/mL versus 1.920 +/- 3.674 µg/mL, $p < 0.001$)²⁰ This was also observed in COVID-19 patients with DVT compared to those without DVT (5.200 +/- 3.000 µg/mL versus 0.800 +/- 1.200 µg/mL, $p < 0.001$).²⁵

III – Should we screen for DVT?

In the midst of the COVID-19 pandemic, specialized teams at Saint-Louis Hospital (Paris) specifically convened to discuss whether it is appropriate to systematically screen for DVT using Doppler ultrasonography (DUS) for early detection and management of thrombosis in COVID-19 patients hospitalized in the departments of pneumology, infectious diseases, and immunology, to prevent further deterioration and admittance to the ICU.

- **In the presence of clinical signs of DVT?**

Recent clinical practice guidelines⁴⁶ strongly recommend the use of a validated VTE prediction tool rather than clinical judgment alone to guide the decision of whether to investigate a potential VTE (Wells score). Several risk assessment models for VTE have been assessed in daily clinical practice, and the Wells score criteria are routinely used for predicting the risk of DVT. The original score published by Wells et al in 1997⁴⁷ used a three-level DVT risk stratification

system (score <1: low probability, score 1 - 2: intermediate probability, score \geq 3: high probability), and included the following parameters: active cancer (undergoing treatment, or received anti-cancer treatment in the previous 6 months or palliative care), paralysis, paresis, or recent cast immobilization of the lower extremities, recently bed ridden \geq 3 days, major surgery within previous 4 weeks requiring general or regional anesthesia, localized pain along the path of the deep venous system, entire leg swelling, increase in volume of the calf by more than 3 cm greater than that of the asymptomatic side (measured 10 cm below tibial tuberosity), pitting edema confined to the symptomatic leg, collateral superficial veins (non-varicose). Two points were deducted from the score if an, at least as likely, alternative diagnosis to DVT was present. A more recent modified version published in 2003⁴⁸ uses two levels of risk stratification (score <2: low probability, score \geq 2: high probability, *appendix 1*) and includes a ninth criterion, namely, a previously documented DVT, and the duration of risk after surgery was increased from 4 weeks to 12 weeks.

In the context of clinical symptoms of DVT, and specifically in the clinical context of prolonged hospitalization for or suspicion of COVID-19 infection, in which patients have been immobile and confined to a bed for long periods of time, the likelihood of a DVT is high, according to the Wells score for VTE.⁴⁸ In this clinical context, DUS of the lower limbs should be performed to assess for DVT when symptoms are present. Concurrent use of thromboprophylaxis, even at the highest dose, does not rule out DVT. Therefore, if there is an onset of DVT symptoms in a patient treated with pharmacological thromboprophylaxis, a Doppler ultrasound must be performed. The diagnosis of DVT will be excluded if the ultrasound scan performed effectively included bilateral and full length examination of the sural and iliofemoral-popliteal venous axes, and that it is negative.⁴⁶

- **In the presence of a PE diagnosed clinically and / or radiologically?**

The French and European 2019 recommendations^{41,46,49,50} on the management of PE in non-COVID-19 patients do not recommend DVT screening in asymptomatic patients.

The PE diagnosis is based on thoracic CT angiography, which is the first-line imaging option in a patient with or suspected of COVID-19, despite the strict hygienic measures necessary between each examination (ie.: cleaning machines, ventilation of the room, protective measures used by medical, paramedical, and technical personnel), and the risk of overwhelming imaging resources. A recent study¹⁹ reported that the delay to confirming a PE diagnosis for COVID-19 patients was

12 days on average from the initial onset of symptoms, despite being a group at highest risk of VTE.^{11,15,23}

Early detection of PE will prompt initiation of anticoagulant treatment at curative doses. In this clinical scenario, additional systematic DVT screening using Duplex doppler ultrasound is not recommended during the COVID-19 pandemic, since the treatment course will be the same whether an associated DVT is also found or not. This hospital clinical consensus was approved by all team members, particularly when considering the risks of exposing healthcare personnel to the SARS-Cov-2 via contaminated materials.

- **In the presence of elevated D-dimer in a patient without clinical symptoms of DVT or PE?**

In patients with COVID-19, with or without VTE, changes in coagulation markers, such as elevated D-dimer levels, are observed during the pulmonary and inflammatory phases.^{11,15,17,20} In non-COVID-related clinical scenarios, a threshold D-dimer level of 500 ng /mL is considered a positive result that confirms elevated levels of the marker. The specificity of this test decreases with age, and the threshold value is adjusted by adding 10 x the number of years beyond the age of 50 years (500 ng/mL + (10 x years over fifty)). This adjustment has been validated and incorporated into updated clinical practice recommendations.^{46,49-51} Given the significant increase in D-dimer levels associated with the inflammatory response in COVID-19, some authors have proposed readjusting the threshold value to 3.000 ng/mL,²⁰ with a sensitivity between 76.9% and 100%, a specificity between 67% and 94.9%, and a negative predictive value of 92.5%.²⁵ Other studies have emphasized the prognostic value of this parameter in patients hospitalized with COVID-19, since an elevated level of D-dimer was significantly more represented in intensive care units than in conventional hospitalization.^{15,19,20,52}

When the clinical probability is low or intermediate based on the Wells scores (Wells score ≤ 2), it is recommended that a D-dimer assay be performed, even if it is frequently high in COVID-19 patients. A negative result will exclude the possibility of a DVT without performing a DUS. In the case of positive D-dimer assay, or in the event of a strong clinical probability (Wells score >2), which would not require the addition of a the D-dimer test, it is recommended to carry out a complete Doppler ultrasound as a diagnostic test for DVT, or in the absence of a feasible full ultrasound, to perform a proximal compression venous ultrasound.

In summary, systematic Doppler ultrasonography for DVT screening in asymptomatic COVID-19 patients is not recommended, unless the patient is in the ICU.⁵³ This would increase the risk

of unnecessarily exposing the medical staff to the SARS-Cov-2 virus and monopolizing limited resources during this period. We recommend that Doppler ultrasonography be prioritized to patients with clinical suspicion of DVT and / or to patients in intensive care. However, an abnormally high D-dimer level ($\geq 3\ 000$ ng /mL) at entry and / or a significant elevation in level during hospitalization should lead be investigated for VTE and lung CT scan angiography will be performed first to search for PE; if negative, even if patient are asymptomatic without clinical symptoms of DVT, DUS should then be performed.

IV - 4-point compression ultrasound: method of choice during the Covid-19 period

The use of 4-point compression ultrasound has been widely used in North America and has been recommended by the American College of Emergency Physicians (ACEP) for almost twenty years.⁵⁴ In France, use of this method has gradually increased in emergency units, and it is now recommended by the French Society of Emergency Medicine,⁵⁵ enabling the emergency physician to detect DVT with a non-invasive method of compression, analyzing the absence of proximal venous incompressibility at the four points (femoral and popliteal, right and left).

The required equipment consists of a standard ultrasound machine (with or without color doppler), typically a high-frequency linear probe (7 to 10 MHz),⁵⁶ ideally combined with a low-frequency convex probe (2 to 5 MHz), which may be useful in the event of significant edema, substantial muscle mass, or in an obese patient. The color doppler is not necessary for performing this ultrasound examination. However, it could prove useful when the compression test is impossible due to edema, pain, or poor echogenicity.

The ultrasound is carried out in mode B, in a transverse plane. This is a bilateral comparative examination which is restricted to a soft progressive compression of the common femoral and popliteal veins (i.e. 2 levels x 2 sides = 4 points), limiting the risk of iatrogenic embolization. This compression test is repeated every 2 cm over a 12 cm segment at each level. The standard criterion for assessing vein permeability is its level of compressibility.^{57,58}

The ultrasound is conducted on a patient in the supine position with trunk and head slightly raised. The patient should externally rotate the hip and have slight flexion of the knee to optimize access to the inguinal region. Localization of the femoral vein is achieved in a transverse plane at the sapheno-femoral Junction ("Mickey ears"), where the common femoral artery, common femoral vein, and great saphenous vein come together. Knee flexion also provides access to the popliteal fossa. The popliteal vein is localized in the popliteal fossa, posterior to the popliteal

artery, and therefore more superficial and closer to the ultrasound probe when using a posterior approach (Figure 2). In the event of difficult examination conditions, the patient can be placed in the prone (or even lateral) position for visualization of the popliteal vein, if necessary. Total or partial incompressibility of the vein (indirect sign) is the only parameter required for a DVT diagnosis.⁴⁶ In the event of a negative proximal ultrasound it is recommended that a complete Doppler examination be conducted within 7 days.⁵⁶

The advantages associated with the 4-point ultrasound are the fact that it is a procedure that is simple, safe (ie.: absence of ionizing radiation), available, inexpensive, reliable (with a sensitivity and specificity in the order of 90 to 100%),⁵⁹ and rapid (between 3 and 5 minutes), limiting potential exposure to the virus and the risk of contamination.

While this method has some limitations, such as the fact that it is 1) not feasible in the prone position, 2) exam operator-dependent, and 3) assessment of the ilio-caval axis and sural veins is not possible,⁶⁰⁻⁶² 4) sensitivity of repeated compression ultrasounds in asymptomatic patients is not known, it is appropriate for use during the Covid-19 pandemic.

V - Impact of COVID-19 on the safety of health care personnel

SARS-CoV-2 is mainly transmitted by air (ie.: respiratory droplets and/or aerosols, coughing) during close contact with a contaminated person (sometimes asymptomatic) or by contact with a contaminated surface.^{63,64} Direct measures such as barrier protection, which includes wearing a surgical mask and protective eyewear, and indirect measures such as hand washing, dedicated wards for COVID-19 patients, and disinfection of equipment and work spaces, can significantly limit the risk of contamination.

The French Society for vascular medicine (SFMV) and the American College of Chest Physicians (CHEST) ²⁴ recently published recommendations for the prevention, diagnosis, and treatment of VTE in patients with COVID-19.⁵³ Furthermore, the Scientific and Standardization Committee has published a communication on the challenges associated with VTE diagnosis in COVID-19 patients.⁶⁵ Designing a care path dedicated to COVID-19 patients with specific schedules and reserved spaces is essential. It will minimize contact between COVID-19 patients and non-COVID-19 patients and reduce the risk of transmission. The implementation of aseptic precautions⁶⁶ is also necessary and should apply to all patients until proven to be COVID-19 negative, and particularly in confirmed or suspected COVID-19 patients.

In order to educate patients, a poster chart should be displayed in the imaging centers conveying that patients have an obligation to report any symptom of COVID-19, wear a surgical mask, wash their hands as they enter the center, not come accompanied by a loved one, limit hand contact with their environment (ie.: door handles, furniture), and pass their own health card (*carte vitale*) and make “contactless” payments using a bank card.

Exposure to SARS-CoV-2 by medical and paramedical staff is repeated and prolonged and they must adequately protect themselves. If a patient has COVID-19 or is suspected of having COVID-19, wearing a surgical mask (at least) is essential. A FFP2 mask should be worn if the healthcare professional is engaged in a treatment that is invasive or requires close contact, such as when performing a DUS of the supra-aortic trunks. A surgical gown and cover gown, a surgical cap, protective glasses, and non-sterile gloves (to be removed between each patient), as well as dedicated clothing (pants, shoes, no watch, or jewelry) are highly recommended. The sonographer will limit contact to a strict minimum, using his right hand for the probe in contact with the patient and his left hand only for the keyboard and the contact gel bottle.

Devices (ultrasound system, all probes with their respective cables) and surfaces that are in contact with the patient (examination table, seats, door handles) should be systematically cleaned with disinfectant or bleach 0.1%, as well as desks, telephones, keyboards and computer mouse between each exam.

Conclusion

In addition to severe respiratory damage due to SARS Cov2, an increase in thromboembolic events has been reported in COVID-19 patients. This increased incidence of thrombosis is still poorly understood but appears to be associated with the unique features of coagulation abnormalities, that are multifactorial (inflammatory syndrome, etc.).

Outside of intensive care, there is no indication for systematic screening for venous thromboembolism in COVID-19 patients in the absence of a clinical symptoms, as outlined by French and European recommendations. This would unnecessarily expose medical and paramedical staff to the risk of contamination and transmission, as well as the risk of hospital-acquired infections in patients. However, systematic D-dimers testing could be a valuable tool in predicting the severity of COVID-19 and the risk of thromboembolic complications.

Thoracic CT angiography appears to be the examination of choice for the screening of PE during a diagnosis of possible pneumonia. The 4-point compression ultrasound is the examination of

choice for the diagnosis of DVT, particularly in the intensive care unit. In the event of a negative test, a complete ultrasound scan is recommended within 7 days. A path of care must be established that will avoid contact between COVID-19 and non-COVID patients. Methodical and systematic disinfection between each patient on the DUS machine is also a priority in restricting contact-mediated contamination and transmission.

Conflict of interest statement: The authors declare no conflict of interest

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Table 1. Incidence of Venous Thromboembolism (VTE, defined as the presence of Pulmonary Embolism (PE) or Venous Thrombo-embolism (VTE)) reported in patients with COVID-19 infection.

Country	N	Study design	VTE prophylaxis	Medical ward	Follow-up duration	DVT	PE +/- DVT
China ²⁵	81	Retrospective cohort	NO	ICU	NR	20/81 (25%)	NR
Netherlands ^{18,29}	184	Retrospective cohort	Nadroparin (weight-adjusted prophylactic dose)	ICU	Median 14 days	1/184 (0.5%)	65/184 (35%)
France ³¹	150	Prospective cohort	105/150 (70%) prophylactic heparin; 45/150 (30%) therapeutic heparin	ICU	Mean 9.6 days	3/150 (2.0%)	25/150 (16.7%)
Italy ⁶⁷	22	Prospective cohort	anticoagulant prophylactic	ICU	NR	5/22 (23%)	NR
France ⁶⁸	26	Retrospective cohort	8/26 (31%) prophylactic heparin, 18/26 (69%) therapeutic heparin	ICU	NR	14/26 (54%)	6/26 (23%)
Italy ⁶⁹	388	Retrospective cohort	175/388 (45%) prophylactic heparin; 17/61 (28%) weight-adjusted prophylactic heparin; 67/388 intermediate dose heparin; 76/388 (19.5%) therapeutic heparin	ICU	Median 18 days	4/388 (0.3%)	10/388 (3.6%)
France ²⁷	107	Retrospective cohort	NR	ICU	NR	2/107 (1.9%)	22/107 (21%)
UK ⁷⁰	63	Retrospective cohort	Weight-adjusted heparin at prophylactic dose	ICU	Median 8 days	0	5/63 (8.0%)
Netherlands ³⁰	198	Retrospective cohort	Nadroparin (weight-adjusted prophylactic dose)	ICU	Median 15 days	25/198 (12.6%)	13/198 (6.6%)
France ⁷¹	71	Retrospective cohort	Weight-appropriate prophylactic Enoxaparin	Non-ICU	NR	22.5%	10%
China ⁷²	88	Retrospective cohort	LMWH) thromboprophylaxis for more than 1 week	ICU	NR	46%	NR
Spain ⁷³	156	Prospective cohort	153 patients received standard dose thromboprophylaxis	Non-ICU	9 days	14.7% (asymptomatic)	NR
China ⁷⁴	143	Retrospective	<ul style="list-style-type: none"> ▪ 53/143 (37.1%), LMWH thromboprophylaxis ▪ 90/143 (62.9%), no thromboprophylaxis 	Non-ICU = 78 ICU = 65	NR	46.1% overall (66/143) <ul style="list-style-type: none"> ▪ 22 (LMWH) ▪ 44 patients (no LMWH) 	NR
Italy ⁷⁵	84	Prospective cohort	Thromboprophylaxis <ul style="list-style-type: none"> ▪ Noxaparin 40 mg once daily ▪ Fondaparinux 2.5 mg daily 	Non-ICU	Mean 5.8 days	11.9%	NR

Figure 1. CT angiogram performed in a 57-year-old patient who tested positive for SARS-CoV-2 in April 2020 and was hospitalized in the infectious disease unit (source: Dr SEBUHYAN Maxime, UF04 Saint Louis Hospital) for acute respiratory failure. **Left panel**, typical of COVID-19 images of the parenchymal window showing ground glass opacities in the lung bases. **Right panel**, mediastinal window showing the presence of a small endoluminal defect in the right lower lobe sub-segment indicative of a pulmonary embolism.

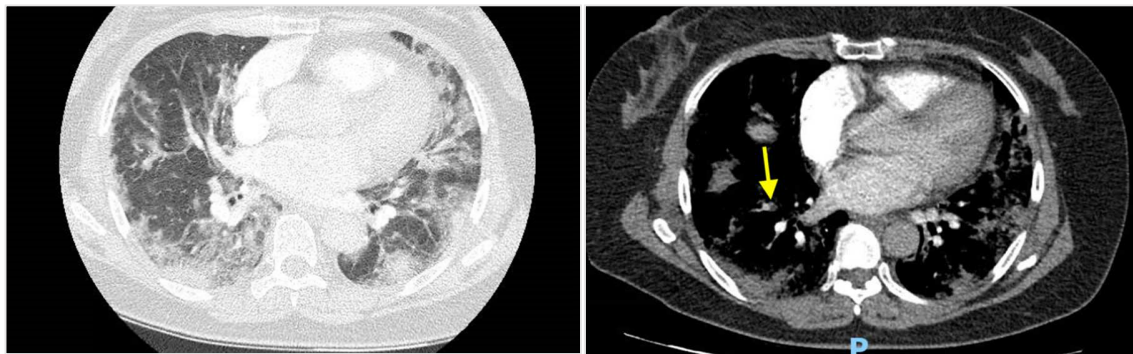
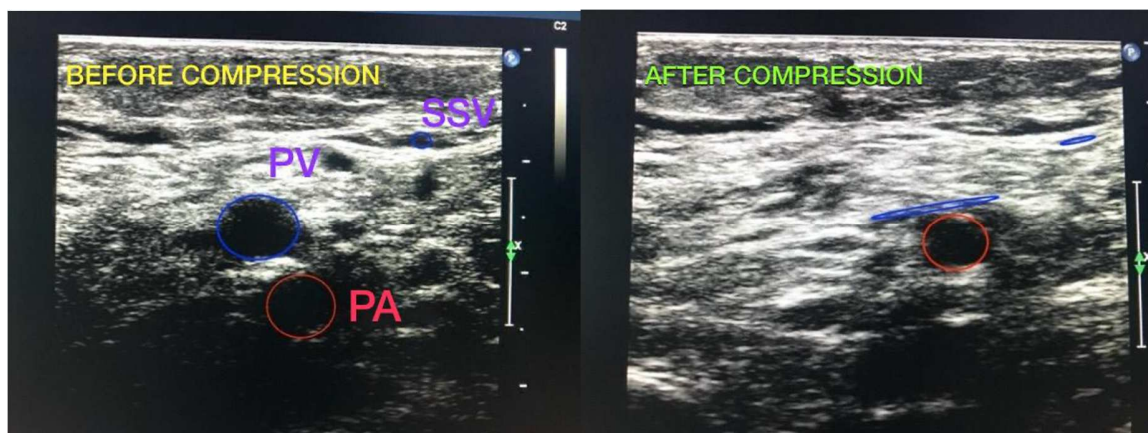


Figure 2. Linear probe compression test, mode B, cross section on the popliteal fossa (source: Dr SEBUHYAN Maxime, UF04 Saint-Louis Hospital, AP-HP). The popliteal vein can be compressed, thereby confirming that this is not a site of thrombosis. The artery is not compressible.



Appendix 1: Two-level DVT Wells score for suspected deep vein thrombosis (DVT) adapted from Wells PS et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003; 349: 1227–35.

Clinical feature	Points	Patient score
Active cancer (treatment ongoing, within 6 months, or palliative)	1	
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1	
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1	
Localised tenderness along the distribution of the deep venous system	1	
Entire leg swollen	1	
Calf swelling at least 3 cm larger than asymptomatic side	1	
Pitting oedema confined to the symptomatic leg	1	
Collateral superficial veins (non-varicose)	1	
Previously documented DVT	1	
An alternative diagnosis is at least as likely as DVT	-2	
Clinical probability simplified score		
DVT <i>likely</i>	2 points or more	
DVT <i>unlikely</i>	1 point or less	