Report on Diagnosis, Prevention and Treatment of Thromboembolic Complications in COVID-19 for the National Institute for Public Health of the Netherlands

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Background

Currently, coronavirus disease 2019 (COVID-19) is spreading rapidly around the globe after it was first recognized in Wuhan, China, in December 2019. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which spreads from human to human primarily via aerosols from coughing or sneezing, but also via contaminated surfaces. SARS-CoV-2 enters cells mainly by endocytosis after binding of its spike glycoproteins to the transmembrane ACE2 protein, which is highly expressed on cells in the lung, but also on cells in the heart, blood vessels, kidney, and gastrointestinal tract. The diagnosis of COVID-19 is confirmed by a positive reverse transcriptase polymerase chain reaction (RT-PCR) from nose, throat, or sputum, although sensitivity of this test is suboptimal ranging from 50-80%, probably due to sampling error or low viral loads, as well as timing of the sample in the course of the disease. In most COVID-19 patients, non-contrast chest CT-scanning shows bilateral ground glass opacities with a peripheral and basal distribution. Notably, sensitivity of CT-imaging is likely to be higher than that of standard RT-PCR.

The current COVID-19 outbreak is unprecedented. Clinicians worldwide face a new disease with high morbidity and mortality, for which no proven therapies are yet available. Based on recent reports that demonstrated a strong association between elevated D-dimer levels and poor prognosis, concerns have risen about thrombotic complications in patients with COVID-19. Therefore, the current committee was given the task to provide an expert opinion on prevention and treatment of thromboembolic complications in patients with COVID-19, and to provide guidance on potential diagnostic and therapeutic interventions. The goal is to improve patient care and decrease the nationwide burden of COVID-19 at intensive care units, hospitals, and other healthcare facilities. The following questions were formulated:

1.1: What is the current state of affairs of research and scientific literature with regard to embolic and thromboembolic complications in COVID-19?

1.2: what practical diagnostic and logistical consequences should follow from question 1.1 according to your expert opinion?

1.3: what therapeutic consequences should follow from 1.1 according to your expert opinion?

1.1: Available Science and Research

A. Current literature on coagulation and thrombosis in COVID-19

Methods
MEDLINE was searched for peer-reviewed publications on COVID-19 and thromboembolic complications. The following search string was used: ("coronavirus disease" OR covid OR covid-19 OR SARS-CoV-2 OR "novel coronavirus" OR “new coronavirus”) AND (D-dimer OR thrombosis OR venous thromboembolism OR pulmonary embolism OR venous thrombosis OR deep-vein thrombosis OR DVT OR deep venous thrombosis OR micro-thrombosis OR disseminated intravascular coagulopathy OR disseminated intravascular coagulation). This search yielded 35 hits on April 8th, 2020.

Summary of current literature
Patients with COVID-19 may develop thrombosis due to hypercoagulability caused by SARS-CoV-2 infection. This can manifest as *venous thromboembolism* (i.e. deep-vein thrombosis and/or pulmonary (arterial) embolism), *disseminated intravascular coagulation* (DIC), and a phenotype of interstitial *pulmonary, vascular congestion, potentially also compatible with venous thrombosis; this entity is referred to as “pulmonary venous thrombosis”*. Or as various combinations of these manifestations.

Venous thromboembolism
None of the studies identified reported on the precise prevalence or incidence of deep-vein thrombosis (DVT) or pulmonary embolism (PE) in patients with COVID-19. Several case reports on concomitant PE in patients with COVID-19 have been published (1). Increasing anecdotal, unpublished information suggests that DVT and PE are regularly detected in patients with COVID-19 (2), in particular in those admitted to the ICU. Case reports also suggests systemic embolism in COVID-19, leading to stroke and myocardial involvement (3,4).

Disseminated intravascular coagulation
One Chinese single-center retrospective cohort study (Tongji hospital) of 183 patients with confirmed COVID-19 evaluated DIC (5). According to the International Society on Thrombosis and Haemostasis definition of DIC, 15 of 21 non-survivors (71%) were classified as having overt-DIC (≥5 points) any time during follow-up whereas only 1 of 162 survivors (0.6%) met these criteria (P<0.001). The median time from admission to DIC was 4 days (range, 2-12 days).

Thrombosis
Recent observations suggest that respiratory failure in COVID-19 may not be driven by ARDS alone, but that (microvascular) thrombotic processes may play a role as well. This may have important consequences for the diagnostic and therapeutic management of these patients. These observations are based on data showing a strong association between D-dimer levels and disease progression as well as radiological features on CT-images suggesting venous thrombo-inflammation.

D-dimer

D-dimer is a degradation product of cross-linked fibrin and reflects blood clot formation and subsequent fibrinolysis. Testing is typically done by either enzyme-linked immunoabsorbent assays (ELISA) or microlatex agglutination assays [6]. D-dimer has a very high sensitivity for thrombotic disease, but its specificity is poor as levels can be increased in a variety of other conditions including cancer, trauma, and infectious disease.

Various studies in patients with COVID-19 have consistently shown a very strong association between increased D-dimer levels and severe disease or poor prognosis (Table 1). Taken together, these observations could reflect: a) disease progression (i.e. increasing viral loads, progressive ARDS, progressive cytokine release) with concomitant DIC, b) differences in management in severe vs non-severe patients (e.g. ICU admission, mechanical ventilation, high vs low PEEP, antiviral therapies), or c) undetected (fatal) thrombotic complications, such as DVT, PE or pulmonary venous thrombosis (PVT).

Table 1. D-dimer levels and their association with disease severity and prognosis in COVID-19

Study	**Baseline D-dimer and COVID-19 disease severity**	**Baseline D-dimer and prognosis**	**D-dimer during follow-up**
Chen et al (7) Single-center retrospective cohort	Severe (N=11): median 2,600 µg/L Moderate: (N=10) median 300 µg/L P=0.029		
Guan et al (8) Multicenter retrospective cohort	Severe (N=109): >500 µg/L in 60% Nonsevere (N=451): P=0.09	ICU, MV, or death (N=49): >500 µg/L in 69% No ICU, MV, nor death (N=511): >500 µg/L in 44% P=0.07	
Tang et al (5) Single-center retrospective cohort		Non-survivors (N=21): median 2,120 µg/L Survivors (N=162): median 610 µg/L P<0.001	Non-survivors (N=21): increase up to 5,000 at day 7 Survivors (N=162): no increase in D-dimer
Zhou et al (9) Multicenter retrospective cohort		Non-survivors (N=54): >500-1000 µg/L in 11% and >1000 µg/L in 81% Survivor (N=137): >500-1000 µg/L in 33% and >1000 µg/L in 24% P<0.0001 Multivariable model (adjusted for age, coronary heart disease, SOFA score, and lymphocyte count: D-dimer >1,000 vs <500 µg/L, OR 18 (95% CI, 2.6-129)	Non-survivors: D-dimer increase up to 42,200 at day 22 Survivors: no increase in D-dimer levels
Wang et al (10) Single-center retrospective cohort		ICU patients (N=36): median 414 µg/L Non-ICU patients (N=102): median 166 µg/L P<0.001	Non-survivors (N=5): D-dimer increase up to 1,000 µg/L at day 13 Survivors (N=28): no increase in D-dimer
Huang et al (11) Single-center retrospective cohort		ICU patients (N=13): median 2,400 µg/L Non-ICU patients (N=28): median 500 µg/L P=0.004	
Li et al (12) Single-center retrospective cohort			Non-survivors (N=12): D-dimer levels increased in 75% of patients during follow-up from a median of 1,180 µg/L to 9,930 µg/L

Pathology findings

Only a few studies have reported on autopsies of deceased COVID-19 patients. A common finding is diffuse alveolar damage (DAD)(13,14). The most recent autopsy report (14)from Beijing describes all SARS1 and SARS2 (COVID-19) patients who have had post-mortem examinations (n= 44/4)(Table 2). They demonstrated diffuse alveolar damage (DAD), pulmonary microvascular thrombosis, and necrosis in lymph nodes and spleen in both patient groups. An important difference between SARS1 and COVID-19 is that in COVID-19 outside the lung system transparent microvascular thrombosis is shown in multiple organs, which is not seen in SARS1, while in SARS1 viral infection is found in multiple organs outside the lung system.

Table 2. Autopsy report post mortem examinations in COVID-19

Comparison of SARS and COVID-19 pathology[14]	
Similarity	**Difference**
Diffuse Alveolar Damage (DAD)	COVID-19 shows type II epithelial cell necrosis, shedding is not as severe as SARS
Lesions at different stages can appear simultaneously	SARS can show AFOP or BOOP, in COVID-19 organizing is less
Alveolar epithelial cells are the main site of viral infection	In COVID-19 multiple organs outside the lung have microvascular transparent thrombus, which is more significant than SARS
Multinucleated giant cells and atypical alveolar epithelial cells	SARS has evidence of viral infection in multiple organs outside the lungs, and COVID-19 has not found evidence of viral infection in extrapulmonary tissues
Pulmonary vascular injury with microvascular thrombosis	
Spleen and lymph node damage, lymphocytes significantly reduced	
Extrapulmonary injury	

B. Interplay between coagulation and COVID-19

The coagulation system can be activated by a variety of different viruses, including HIV, Dengue virus, and Ebola virus (15,16). During the relatively recent outbreak of SARS-CoV in 2003, which was associated with even higher morbidity and mortality than COVID-19, vascular endothelial damage in both small- and mid-sized pulmonary vessels was noted together with DIC, DVT and PE resulting in pulmonary infarction (17-20). In fact, a case report of an autopsy described thrombosis in multiple organs in a patient with proven SARS-CoV infection (21). Given the similarity between SARS-CoV and SARS-CoV-2, similar thrombotic complications are likely to be present in patients with COVID-19. Whether the coagulation cascade is directly activated by the virus or whether this is the result of local or systemic inflammation is not completely understood.

In COVID-19, high plasma levels of proinflammatory cytokines (interleukin-2, interleukin-7, granulocyte colony-stimulating factor, IP10, MCP1, MIP1A. and tumor necrosis factor-α) have been observed in patients admitted to intensive care units, suggesting that a cytokine storm effect may be developing in individuals with severe disease with a secondary hemophagocytic lymphohistiocytosis (7,22). While many pro-inflammatory cytokines trigger the coagulation system, the study by Zhou and colleagues (9) showed that the increase in IL-6 was discrepant with the elevations in D-dimer; IL-6 levels appeared to increase only 13 days after disease onset, whereas D-dimer levels were already 10-fold increased by that time. This observation

suggests that the very high D-dimer levels observed in COVID-19 patients are not only secondary to systemic inflammation, but also reflect true thrombotic disease, probably induced by local, cellular activation, triggered by virus infiltration. Although the lower platelet count and longer prothrombin times observed in patients with severe COVID-19 suggest that DIC might be present, at the same time (pulmonary) venous thrombosis, DVT, and/or PE may be present.

Role of antithrombotic therapy

Notably, a Chinese single-center retrospective cohort study (Tonghi hospital) of 449 consecutive patients classified as having severe COVID-19 indicates that prophylactic doses of heparins might be associated with improved survival (20%) in patients with evidence of sepsis induced coagulopathy (SIC)/DIC (23). Severe COVID-19 was defined as either a respiratory rate ≥30/min, arterial oxygen saturation ≤93% at rest, or PaO2/FiO2 ≤300 mmHg. Exclusion criteria included bleeding diathesis, hospital stay <7 days and lack of information of coagulation parameters and medications. Of the 449 patients, 99 (22%) received heparin for 7 days or longer (LMWH in 94 patients, usually enoxaparin 40-60 mg/day, and UFH in 5). Heparin was associated with lower 28-day mortality among the 97 patients with a SIC score ≥4, (40% vs 64%; OR, 0.37 [95% CI, 0.15-0.90]; P=0.029), but not among the 352 patients with a SIC score <4 (29% vs 23%; P=0.42).

C. Imaging in the COVID-19

Introduction

Patients with COVID-19 demonstrate a newly recognized spectrum of abnormalities on chest CT. The reporting of COVID-19 CT is increasingly standardized to allow for improved identification and risk stratification through quantification of abnormalities. Comorbidity and alternative diagnoses are also registered, as symptoms can of course point to other diseases. Several proposals have been made to enable standardized reporting, such as CO-RADS by the Dutch Radiological Society (24) and a consensus statement from USA colleagues (25). Typical characteristics and time course of lung changes on chest CT were recently described (26). The CT severity score on initial scans is based on the amount of lung tissue (% lung parenchyma) that is involved at presentation (27).

CT findings in COVID-19

Chest CT features were described in a cohort of 1014 patients in Wuhan, China (28). Ground glass opacities (GGO), defined as increased density with preservation of background lung texture, were found in all patients (100%) and confirmed by the chest CT findings observed in 158 consecutive patients from Italy (29).

"In this study GGO were present in 58/58 patients (100%), multilobe involvement (≥ 2 lobes) and posterior involvement were both present in 54/58 (93%) patients, 53/58 (91%) patients had bilateral pneumonia, and peripheral GGO was observed in 52/58 (89%). Simultaneous involvement of all five lobes was observed in 43/58 patients (74%). The right lower lobe was the most affected in 53/58 patients (93%), followed by left lower lobe and the right upper lobe involved in 51/58 patients (both 91%). Regarding GGO, three patterns were observed in order of frequency as follows: "Crazy" paving in 23/58 patients (39%), rounded morphology in 19/58 patients (32%) and linear opacities in 16/58 cases (27%). An enlarged subsegmental vessel, defined as vessel diameter > 3 mm, was observed in 52/58 patients (89%) with mean vessel diameter of 3.9±0.6 mm. Consolidation was observed in 42/58 patients (72%) including 32/58 (55%) with subsegmental involvement.

Presence of lymphadenopathy was reported in 34/58 patients (59%). Chest CT features were compared between patients who required hospitalization (inpatients, 49 patients) versus those patients who were referred for home isolation (outpatients, 9 patients). There were no significant differences in chest CT findings between these groups, all findings p>0.06).”

The typical CT pattern of COVID-19 pneumonia in Rome, Italy was characterized by the consistent presence of peripheral ground glass opacities associated with multi-lobar and posterior involvement, bilateral distribution, and subsegmental vessel enlargement. Vessel enlargement was described in the vicinity of areas with GGO, which is compatible with thrombo-inflammatory processes (29–31). Subsegmental vascular enlargement (more than 3 mm diameter) in areas of lung opacity was observed in 89% of patients with confirmed COVID-19 pneumonia. Although there is no mention of dilated vessels in studies from the USA, the study from Italy describes vessel enlargement in 43/49 CT patients. The authors do not indicate whether these vessels are arteries or veins and it is difficult to be certain from the limited images in the publication. All the CT’s were done without contrast. Although in situ thrombosis is certainly a possibility, the findings could be due to hyperemia and increased blood flow.

Vessel enlargement is also described by Albarello et al in two patients in Italy (32). Bai et al described subsegmental vascular enlargement in 59% of the patients with COVID-19 pneumonia versus 22% of those with non-viral pneumonia (33). Ye et al suggested vascular enlargement may be due to pro-inflammatory factors (34). Subsegmental vascular enlargement could reflect the hyperemia induced by SARS-CoV-2 infection, which is in contrast with viral pulmonary infections such as SARS and MERS (35,36). If CT does not show GGO abnormalities COVID-19 is unlikely. *Thus, non-contrast enhanced CT provides earlier manifestations of COVID-19 in patients where PCR is still negative*.

Some case reports on FDG PET/CT confirm the inflammatory component of the GGOs (37).
Furthermore, with disease progression and immobilization, the incidence of DVT and PE will increase. Several case reports mention PE in peripheral as well as central pulmonary vessels in the development of COVID-19 (1,2). A recent retrospective study in 1008 patients, in which 25 patients underwent CT pulmonary angiography, demonstrated acute PE in 10 patients (40%), which were mainly located in subsegmental vessels. All patients were treated with anticoagulant therapy, and three demonstrated partial or complete resolution at follow-up CT pulmonary angiography, while two patients died (2).

Taken together, based on these studies, both pulmonary thrombo-inflammatory processes, systemic-thrombosis and PE are currently poorly evaluated on chest CT examinations when contrast is not given. In the later stages of the illness, there are no clinical CT investigations with intravenous contrast in patients who become respiratory insufficient. This is often due to technical challenges and difficult to manage patients by nursing staff and radiological technicians, and due to a combination of severely ill patients who are also highly contagious. Therefore, in late phases it is often regarded as poorly feasible to diagnose thromboembolic disease or complications. Importantly, this is a phase where plasma D-dimer may become extremely elevated in those with thrombo-inflammatory underlying pathophysiology (8).

Figure 1

Figure 1 gives a schematic representation of the pathophysiological disease development of COVID-19, based on the results in the Wuhan population in the context of plasma D-dimer values, clinical and imaging characteristics (reconstructed from Zhou et al 2020).

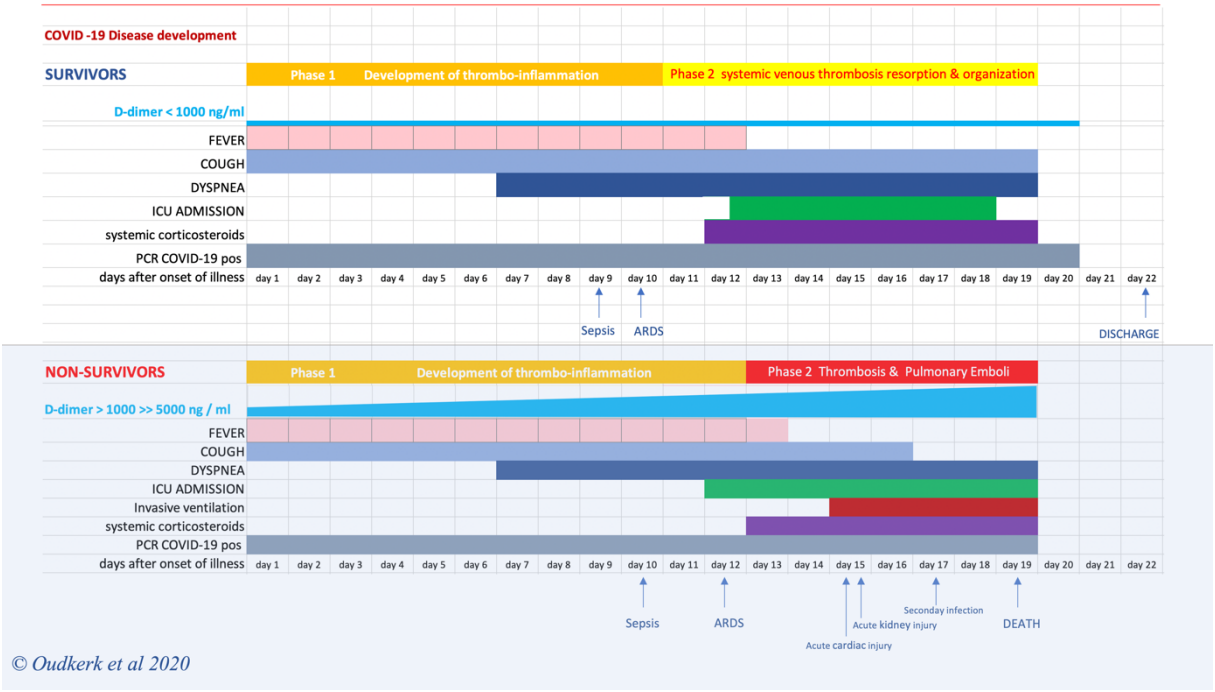
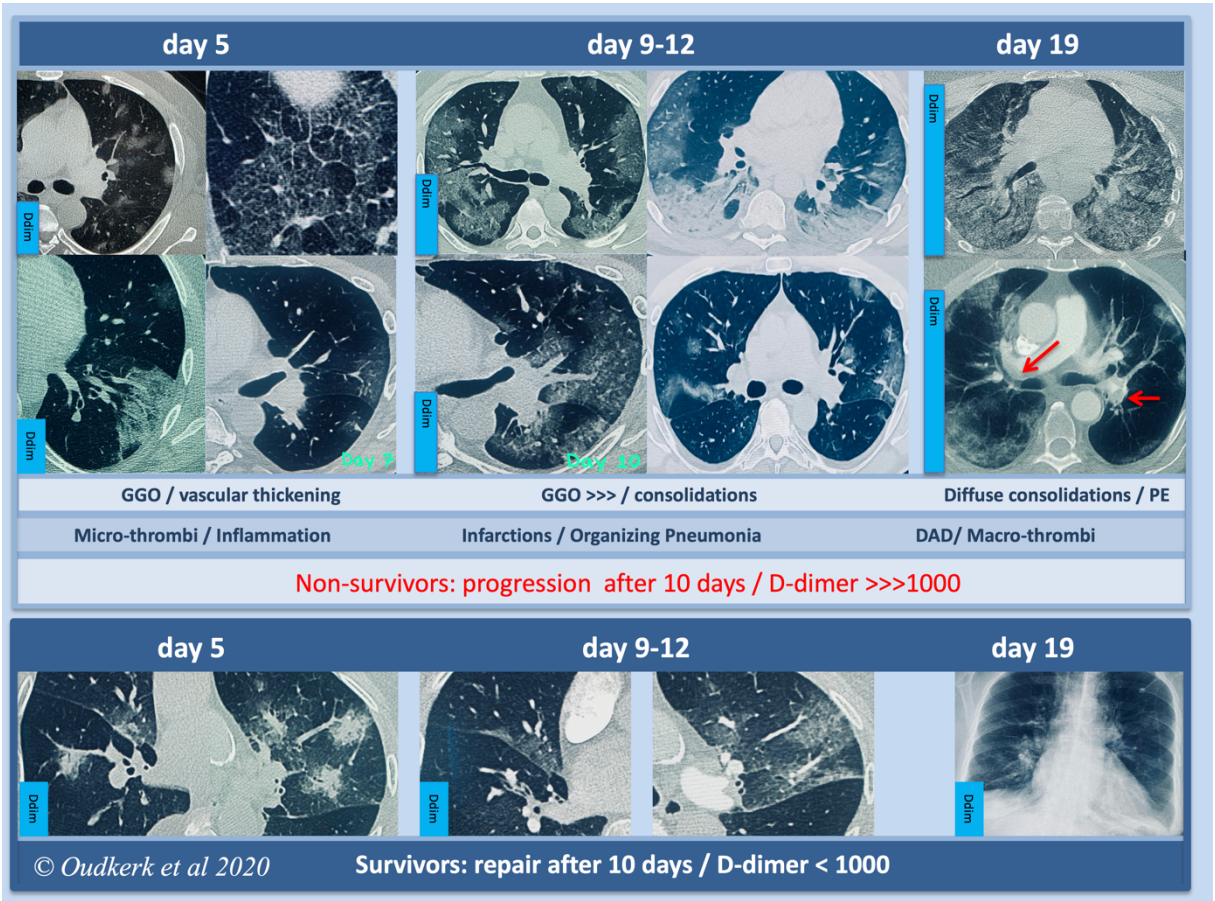


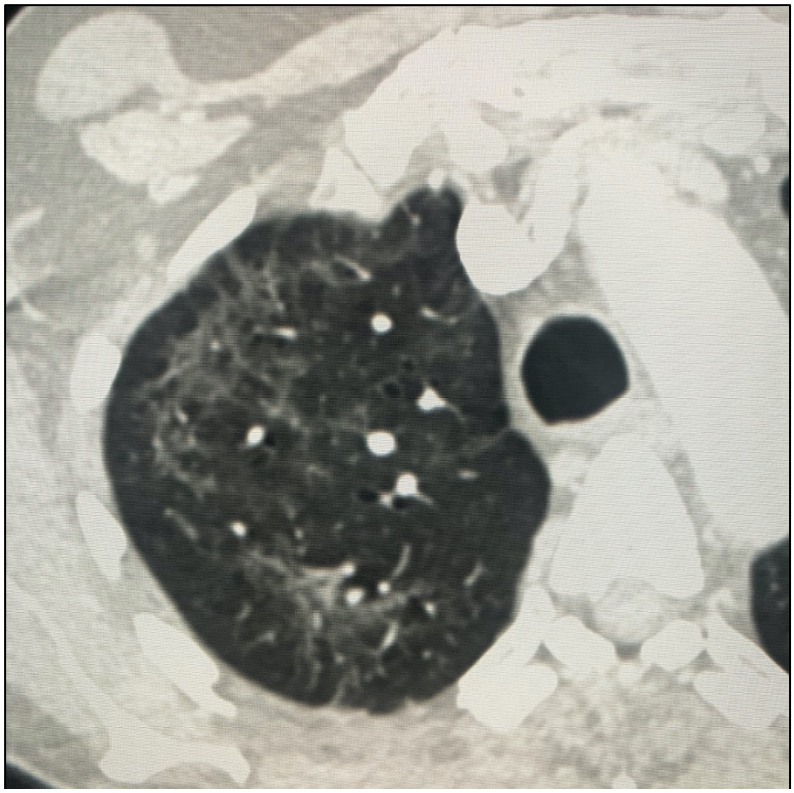
Figure 2

Figure 2 represents the CT chest findings along the same timeline of COVID-19 development as Figure 1 in non-survivors (top row) and survivor patients (bottom row).

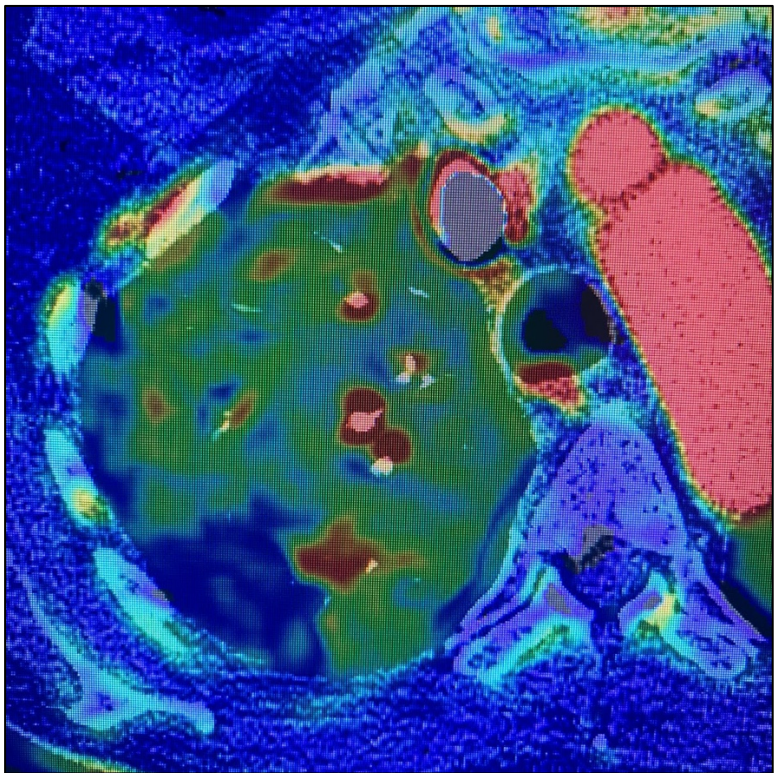


GGO: Ground Glass Opacities; PE: Pulmonary Embolism; DAD: Diffuse Alveolar Damage

Figure 3 PROOF OF CONCEPT Preliminary findings of CT Perfusion in phase 1 show perfusion defects in a patient with multiple GGO's, without pulmonary emboli on CT pulmonary angiography.



Native chest CT shows multiple GGO in the right lung



CT Perfusion shows multiple perfusion deficits (blew areas)

1.2 and 1.3 Diagnostic and Therapeutic Management

1. Prophylactic-dose low-molecular-weight heparin should be initiated in all patients with (suspected) COVID-19 admitted to the hospital, irrespective of risk scores (e.g. Padua score).
2. A baseline (non-contrast) chest CT should be considered in all patients with suspected COVID-19 who have an indication for hospital admission (Dutch Healthcare).
3. In patients with suspected COVID-19 as well as a high clinical suspicion for PE (e.g. based on hemoptysis, unexplained tachycardia, or signs/symptoms of DVT, acute deterioration upon moving patient), CT pulmonary angiography should be considered if the D-dimer level is elevated. The D-dimer threshold used should follow locally used algorithms, i.e. ≥500 mg/L, age-adjusted threshold, or ≥1,000 mg/L when no YEARS criteria are present. If PE is confirmed, therapeutic anticoagulation is indicated.
4. In patients with COVID-19 admitted to the hospital, routine D-dimer testing on admission and serially during hospital stay should be considered for prognostic stratification.
    a. In patients with a D-dimer <1,000 µg/L on admission and no significant increase during follow-up, prophylactic anticoagulation should be continued.
    b. In patients with a D-dimer <1,000 µg/L on admission but a significant increase during hospital stay to levels above 2,000-4,000 µg/L, imaging for DVT or PE should be considered, in particular when signs suggestive of clinically-relevant hypercoagulability such as venous congestion/thrombosis are present on chest CT, clotting of extracorporeal circuits, or when patients deteriorate clinically (e.g. refractory hypoxemia or unexplained new-onset tachycardia or hypotension). When imaging is not feasible, therapeutic-dose low-molecular-weight heparin without imaging can be considered when the risk of bleeding is acceptable.
    c. For patients with D-dimer values between 1,000 and 2,000 µg/L, there is no clear-cut guidance other than institution of prophylactic anticoagulation. These patients may suffer from venous thromboembolism, and where possible this should be excluded. Close monitoring of D-dimer in combination with clinical findings should lead to further decision making along the lines of low vs strongly increased D-dimer levels.
    d. In patients with a strongly increased D-dimer on admission (e.g. 2,000-4,000 µg/L), caution is warranted. D-dimer testing should be repeated within 24-48 hours to detect further increases in which case imaging for DVT or PE should be considered as outlined above.

Signed for approval Groningen, April 9 2020

Matthijs Oudkerk

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