Coagulation disorders in adults with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a scoping review

Problemas de coagulação em adultos com síndroma respiratório agudo grave devido a infeção por coronavírus 2 (SARS-CoV-2): uma revisão abrangente

Supplementary Material

SUPPLEMENTARY TABLE 1. Synthesis of results

Statement	References
1. Characterization of coagulation disorders	
Coagulation dysfunction is common in patients with COVID-19.	12,24,26,29,33,64-66
Different thromboembolic events, including VTE, have been noticed since the beginning of COVID-19 pandemic.	19,23,30,36,38,50,56,64, 67-69
Among VTE, PE has been particularly noticed in the context of COVID-19 pandemic.	19,23,36,38,47,51,60,68, 70-73
IS is counted among those different thromboembolic events that have been noticed since the beginning of COVID-19 pandemic.	29,36,38
ACS seems to be one of the thromboembolic events associated to COVID-19 pandemic.	36,38,66,74-77
DIC has been noticed to be associated to SARS-CoV-2 infection.	17,22,36,38-39,78-79
The incidence of thrombosis in infected patients has not been determined yet.	29
About 20% to 55% of patients admitted to hospital for COVID-19 show laboratory evidence of coagulopathy.	65
Thromboembolic events occurred in 7.7% (95%CI [5.4%-11.0%]) of admitted patients, corresponding to 6.4% (95%CI [4.2%-9.6%]) in the general ward and 16.7% (95%CI [8.7%-29.6%]) in the ICU.	36
Confirmed COVID-19 cases admitted to ICU stated a prevalence of 31% of vascular thrombosis, which was most frequently (81%) seen in pulmonary vessels.	19
VTE were reported in two out of nine patients admitted to ICU due to SARS-CoV-2 with interstitial pneumonia.	68
Coagulation dysfunction in COVID-19 patients may represent an under-estimated large-scale issue.	36,74
The burden of thromboembolic complications in ambulatory patients is still unknown.	36
The coagulopathy associated to SARS-CoV-2 infection has been correlated with disease severity.	66,72,80-81
The risk of thrombosis in COVID-19 patients is especially important in those who have serious underlying conditions.	17,23,29-30
Obesity is one of the conditions that increases the risk of thrombosis in COVID-19 patients.	29-0
Diabetes is associated to increased risk of thrombosis in COVID-19 patients.	28
Heart failure increases the risk of thrombosis in COVID-19 patients.	30,76-77
Respiratory failure, chronic kidney disease, previous thrombosis history, acute cerebral infarction, ACS, varicose vein of lower extremity, acute onset of chronic obstructive pulmonary disease, inflammatory bowel disease, and malignant tumor are counted among those conditions that increase the risk of thrombosis in COVID-19 patients.	30
Immobilization is an independent risk factor for thrombotic events in COVID-19 patients.	23,29,30

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Old age is also an independent risk factor for thrombotic events in COVID-19 patients.	29-30
Disease severity has been correlated with older age.	12,75,82-83
Older age was the only independent predictor of mortality.	75
a. Venous thromboembolism	
Systemic inflammation, abnormal coagulation status, MOF, and critical illness are all potential contributing factors to the increased risk of VTE.	64
The most frequent localization of the thrombus is the iliac-femoral-popliteal axis, followed by the brachial-axillary veins and the calf veins.	69
Compression ultrasound scans of the venous system, performed on both lower and upper limbs, of COVID-19 non-ICU patients with suggestive signs or symptoms showed that 16 non-ICU patients had positive results and six more had superficial thrombophlebitis or upper limb lymphedema.	69
VTE was only found in critical patients, with a prevalence of 16 out of 36 patients with COVID-19 pneumonia.	67
b. Pulmonary thromboembolism	
The evidence is insufficient to establish a firm association between PE and COVID-19.	73
A prevalence of 23% of acute PE in patients with COVID-19 was reported.	70
An estimated 1.3% higher rate of PE than the usually encountered in critically ill patients without SARS-CoV-2 infection, or in emergency department patients (3 to 10%) was found.	84
These patients, mainly of male gender, are more likely to require care in the ICU and mechanical ventilation than those without PE.	70
PE is usually diagnosed around 12 days from symptom onset.	70
PE should be considered in COVID-19 patients with reduced blood pressure.	23,50
PE should be considered in COVID-19 patients with sudden onset of oxygenation deterioration.	23,37,47,50,77
PE should be considered in COVID-19 patients with respiratory distress.	23,37,47,50
Sudden deterioration in respiratory status that is not explained by significant radiological changes in the lung fields, and especially in conjunction with high titers of D-dimers, should raise suspicion for pulmonary embolism.	47
Clinicians should also consider looking for PE in patients with COVID-19 pneumonia who have travelled on long-haul flights.	60
It could be possible that PE may further complicate the course of COVID-19 pneumonia.	79
On histopathologic findings of pulmonary biopsy of critical patients with COVID-19 pneumonia, small vessels hyperplasia, vessel wall thickening, lumen stenosis, occlusion, and micro-thrombosis formation have been described.	19
Although the biological mechanisms underlying COVID-19 pulmonary-vasculopathy remain poorly understood, the ACE-2 receptor utilized by COVID-19 is expressed on both type II pneumocytes and vascular endothelial cells within the lungs, raising the interesting possibility that the pathobiology may include direct pulmonary endothelial cells infection, activation and/or damage.	81
We cannot exclude that coagulation disorders occur mainly in pulmonary microcirculation, which may also be the pathophysiological mechanism underlying the reduction of oxygenation.	27
A major risk of pulmonary artery micro-thrombosis, associated to a novel pulmonary-specific vasculopathy, termed pulmonary intravascular coagulopathy has been described.	38,81
The pulmonary abnormalities appear largely restricted to the alveolar capillaries with a thrombotic microvascular injury similar to a local DIC.	18,79
The pulmonary abnormalities are more frequent in critically-ill patients.	85
Although hemoptysis has been described as an infrequent COVID-19 clinical symptom (0-5%), it was presented as one of the clinical features with the highest association with PE.	26

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
2. Ischemic stroke	
The incidence of cerebral infarction in patients with severe COVID-19 reaches 4.5%, which may be related to the underlying diseases of critically ill patients.	29
3. Acute coronary syndrome	
The risk of ACS due to extensive inflammation and hypercoagulability is likely present in patients with COVID-19.	64
Once COVID-19 patients present severe pneumonia, myocardial ischemia or cardiac dysfunction are more likely to occur.	76
A statistically significant association between cardiac injury and mortality was found in these patients (51.2% *vs* 4.5%; $p<0.001$).	76
Even though the mechanism of cardiac injury among patients with COVID-19 is still uncertain, inflammation is thought to cause endothelial dysfunction and to increase procoagulant activity of the blood, which can lead to the formation of an occlusive thrombus over a ruptured coronary plaque.	76
Cytokines released during the acute infection can elicit activation of cells, augmenting the risk for thrombotic and ischemic syndromes in those patients with pre-existing atherosclerotic lesions.	66
4. Disseminated intravascular coagulation	
Emerging data support that infected patients are at risk of developing DIC.	12,39,72,79
The incidence of DIC increases with the progression of COVID-19.	78
DIC occurs in 74.1% of non-survivors and 0.6% of survivors.	31
A defective pro-coagulant-anticoagulant balance causes coagulation dysfunction.	22
The excessive depletion of coagulation substrates causes coagulation dysfunction.	17
Coagulation dysfunction can lead to a consumption coagulopathy.	29,39
Coagulation dysfunction can lead to the development of DIC and MOF.	17,22
DIC is linked to a worse prognosis.	72
Diagnosis of DIC is often delayed until bleeding from multiple sites occurs.	29,79
No bleeding complications were recorded on specific studies.	24,36
The ISTH suggests the systematic use of diagnostic criteria, rather than just relying on clinical manifestation for DIC diagnosis.	29,40,79
As none isolated parameter is sensitive or specific enough for the diagnosis of DIC, a two-stage method has been created to early diagnose coagulation disorders related to sepsis or DIC. The first stage consists in using the sepsis-induced coagulopathy integration system to rapidly identify the hypercoagulability period and begin anticoagulation therapy. The second stage is the use of DIC scoring system to monitor the situation and guide the treatment.	29
The parameters of DIC diagnostic scoring system include PT, platelet count, fibrinogen, and D-dimers. A score of 5 or higher is diagnosed as overt DIC and less than 5 is diagnosed as non-overt DIC, which would need to be evaluated daily.	17
5. Other thromboembolic events	
The occurrence of thrombotic formation attached to the tricuspid valve in the absence of predisposing factors and fatal cardiac arrest with pulseless electrical activity have been described in COVID-19 patients.	68
Acute arterial thrombosis of lower limb, for which the underlying cause was arteriosclerosis obliterans of lower extremity, has also been mentioned in COVID-19 patients.	30
Other cases of patients having multiple location thromboembolism have been reported as well, such as bilateral lobar pulmonary emboli, new left renal infarct, occlusion of the distal basilar artery and small thrombus in the aortic arch.	80

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Vascular lesions were reported in some patients, with eruptive chilblain lesions during spring and containment that may be a new symptom revealing a pauci-symptomatic COVID-19.	86
6. Pathophysiology	
COVID-19 has been well described as responsible for proinflammatory and hypercoagulation state.	23,26-27,38-39,62,71, 77-78,87-88
COVID-19 predisposes patients to thrombotic disease due to excessive inflammation, endothelial dysfunction, platelet activation, and stasis.	53
a. Inflammation	
There is a close connection between thrombosis and inflammation.	39
Viral infections elicit the systemic inflammatory response and cause an imbalance between procoagulant and anticoagulant homeostatic mechanisms.	12,72
In SARS-CoV-2 infection, inflammatory reactions occur in all organs of the body, damaging the microvascular system which lead to abnormal activation of the coagulation system, that pathologically manifests as generalized small vessel vasculitis and extensive microthrombosis.	17-19
Thrombin also exerts multiple cellular effects by promoting clot formation and can further augment inflammation via PARs, mainly PAR-1.5.	22
Thrombin generation is tightly controlled by negative feedback loops and physiological anticoagulants, such as antithrombin III, tissue factor pathway inhibitor, and C protein system.	22
Thrombin generation can be impaired, by reduced anticoagulant concentrations due to reduced production and increasing consumption.	22,75
b. Endothelial disfunction	
Coronavirus causes inflammation-mediated endothelial injury.	19
Coronavirus causes direct endothelial cell injury to the micro-vessels, with subsequent release of damaged endothelial cells into the bloodstream.	23
Endothelial injury is often mentioned as one of the pathophysiological mechanisms underlying in thromboembolic events associated to SARS-CoV-2 infection.	12,18,23,29,53,75,77, 79,83
Inflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha are also considered to be pathophysiological mediators of thromboembolic events associated to SARS-CoV-2 infection.	66,75
Endothelial injury and inflammatory cytokines are known to upregulate tissue factor expression.	12,75,89
Endothelial injury and inflammatory cytokines drive to a prothrombotic state by upregulating tissue factor expression.	29,89
Remarkably, the dysfunctional endothelium becomes pro-adhesive and pro-coagulant too.	83
c. Platelet activation	
Platelets are key mediators of inflammation and sensors of infectious agents through the interaction of cell surface receptors and pathogens or immune system derivatives.	12
Upon antigen recognition, they become activated and interact with white blood cells to facilitate pathogen clearance through white blood cell activation and clot formation.	12
Likewise, platelet activation also ensues in the context of sepsis and inflammation, further tipping the fine balance of the coagulation system.	75
Disruption of coagulation balance is manifested by platelet peaks and seems to be responsible for increasing the duration of hospitalization in older patients.	90
One of the clinical results of this activation is platelet aggregation, platelet consumption and, consequently, thrombocytopenia, which is observed frequently in patients with severe COVID-19. However, the latter can also be explained by three other possible mechanisms: direct infection of bone marrow cells by the virus, inhibition of platelet synthesis due to destruction of bone marrow progenitor cells by cytokine storm, and platelet destruction by the immune system.	91

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
d. Other factors	
SARS-CoV-2 is likely to promote massive fibrin formation and deposition.	72,74,89
Fibrin formation and deposition is due to increased plasmin concentration.	72
Thrombocytopenia can be explained by the excessive activation of platelets and of the coagulation cascade.	12,17,91
Elevated D-dimers can also be explained by the excessive activation of platelets and of the coagulation cascade.	12,17,22,64,72,74,87,89
The excessive activation of platelets and of the coagulation cascade can also account for other coagulation abnormalities (such as increased levels of fibrinogen, fibrin and FDPs and reduced levels of antithrombin, when compared to the healthy control population).	12,17,72
Multiple other pathogenic mechanisms are involved, including VWF elevation and toll-like receptor activation.	12
There are also potential mechanisms of complement activation, including involvement of positive feedback loops with the coagulation system.	18
Although complement does not appear to play a major role in controlling virus replication, it may have a critical role in its pathogenicity.	18
Rarely, the presence of antiphospholipid antibodies may also lead to thrombotic events. Yet, those are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as DIC, heparin-induced thrombocytopenia and thrombotic microangiopathy.	92
7. Laboratory diagnosis	
The use of simple and easily available laboratory markers, both at admission and while in the hospital, is necessary for the management of COVID-19 patients.	63
There are conflicting opinions on whether to perform a coagulation test screening.	25
It is recommended to perform a coagulation test screening including D-dimers, PT, aPTT and fibrinogen in hospitalized COVID-19 patients.	17,24
The coagulation test screening should also include a complete blood count, biochemistry tests, in addition to inflammation markers, electrolyte determination, liver function, and markers of renal and cardiac damage.	93
Monitoring platelet count could also help to rapidly and accurately predict disease outcomes and good prognosis of COVID-19 and to identify patients at a higher risk for thromboembolic events.	93-95
Routine monitoring of D-dimers and other useful tests such as PT, aPTT, fibrinogen and platelet count could help to rapidly and accurately predict disease outcomes and good prognosis of COVID-19 and to identify patients at a higher risk or those who have already developed DIC.	93
For rapidly and accurately predicting disease outcomes and good prognosis of COVID-19 and for identifying patients at a higher risk or those who have already developed VTE, routine monitoring of D-dimers and other useful tests can be performed.	56,93
Monitoring of coagulation status by laboratory tests is especially useful when manpower and access to CT are limited.	63
a. D-dimers	
D-dimers are elevated in non-severe patients with COVID-19.	24,33,88,96
The percentage of COVID-19 patients with elevated D-dimers varies from 36 to 50% in some series.	12,29,47,72
In severe COVID-19 cases, the percentage of patients having elevated D-dimers is significantly more elevated.	12,38,75,89,97
In severe COVID-19 cases, the percentage of patients having elevated D-dimers can reach 60%.	41
The magnitude of elevation of D-dimers in severe COVID-19 patients increases the probability to develop thrombosis and progressive coagulation activation.	17,31,81,84,98

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
D-dimers greater than 500 µg/L at admission have been correlated with a more severe disease.	99
D-dimers at admission have been correlated even with occurrence of death when greater than 1000 µg/L.	26,82,99
A concentration four times above normal has also been associated to an approximately fivefold higher odds of critical illness than a normal D-dimer concentration.	100
The fast-increasing D-dimer levels observed in non-survivors could reflect the inflammatory and procoagulant state of COVID-19.	36
In patients with D-dimers lower than 1000 µg/L on admission but with a significant increase during hospital stay to levels above 2000-4000 µg/L, imaging evaluation for VTE or PE was proposed, in particular when signs suggestive of clinically relevant hypercoagulability are present.	37
Increased D-dimer levels have been identified as an independent risk factor for the development of ARDS, ICU admission and death in COVID-19 patients.	17,39,42,75,83
The difference in median D-dimers between the death and survival groups was larger than that between the ARDS and non-ARDS groups, which implies that DIC may be related to mortality in some patients.	83
b. PT and aPTT	
Evidence of significant prolonged PT was observed in critically ill patients suggesting its relation to DIC.	31,48,65,89,98
On the opposite, among non-critical COVID-19 patients, levels of PT and aPTT were only rather modestly altered.	31
c. Fibrinogen	
Although studies corroborate a marked elevation of fibrinogen in mild COVID-19 cases and in the initial stage of critically ill patients, they also show significantly reduced levels in the advanced stages of critically ill patients or late disease.	24,29,31,65
Fibrinogen levels seem to decrease after increasing thromboprophylaxis.	62
As the disease recovers, fibrinogen levels also return to normal.	33,62,74
d. Fibrinogen degradation products (FDP)	
Increased levels of FDPs are described as one of the main characteristics of the abnormal coagulation pattern in severe-type and even more in critical-type COVID-19 patients.	89
e. Platelets	
SARS-CoV-2 infected patients commonly develop thrombocytopenia.	29
The determined prevalence of thrombocytopenia in infected patients ranges between 20.7% and 36.2%.	12,94
Thrombocytopenia is relatively uncommon in initial presentations.	24,41,65,81,101
In non-severe patients it has been reported a mild thrombocytopenia (platelet count over 100×10^9/L).	65
In critically-ill COVID-patients, even a more severe thrombocytopenia is observed.	95
Platelet counts less than 50×10^9/L are extremely rare in COVID-19.	94
Thrombocytopenia at admission was associated to almost three times higher mortality than in patients with a normal platelet count.	102
Dynamic changes of platelets were closely related to death during treatment.	102
Platelet count may be an independent risk factor for COVID-19 mortality.	102
Monitoring platelet counts in COVID-19 is paramount since a decrease after an initial surge may suggest the start of a process which may be harmful to the host. For the same reason, improvement of the platelet counts may signify imminent clinical improvement.	91,94
The 'higher' platelet counts are unusual for an illness as severe as COVID-19 and likely point towards liver activation and thrombopoietin release following pulmonary inflammation.	103

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
f. Other parameters	
Viscoelastic tests have been used to evaluate coagulation function of severe COVID-19 patients aiming to give relevant information to early diagnosis and timely intervention. aPTT-based clot waveform analysis parameters markedly raise as ICU stay progressed. As well, as patients' clinical conditions turn critical, min1 seem to be the first CWA parameter to rise.	17,29
In one study, all patients had high C-reactive protein levels even on initial assessment during hospitalization, while procalcitonin remained unremarkable.	104
All critically-ill COVID-19 patients had elevated values of IL-6, and a clear association between IL-6 and fibrinogen levels was demonstrated.	62
Other studies showed an elevation of IgM anti-cardiolipin antibodies and antibeta2-glycoprotein I.	97
A massive elevation of VWF and an increase of factor VIII clotting activity was remarked during ICU stay.	105
8. Imaging diagnosis	
a. Lung ultrasound	
Lung ultrasound can serve as a valuable tool for the detection and follow-up of lung lesions in COVID-19 pneumonia and also provide supplemental imaging information for current recommended radiological examination, with the advantages of radiation-free, flexibility, and cost-effectiveness.	67
Patients with elevated D-dimers and subpleural consolidations in lung ultrasonography, might be advised to do a diagnostic workup of a potential PE.	106
Point of care ultrasound might be helpful for clinicians in identifying COVID-19 patients at risk for concurrent PE.	26
b. Vascular ultrasound	
A close vein ultrasound screening and monitoring should be performed to all patients hospitalized due to SARS-CoV-2-related infection.	68
A vein ultrasound screening and monitoring of both lower extremities should be performed in patients with COVID-19 with significant elevation of FDPs and D-dimers.	107
c. Chest CT angiography	
Several clinical reports showed bilateral lobar pulmonary emboli in chest CT in COVID-19 patients.	60,73,80,108
There is a strong association between chest CT venous thrombosis features, D-dimer levels and disease progression.	19,23,29,37,72
In patients with COVID-19 pneumonia presenting with worsening of clinical respiratory symptoms, chest CT angiography should be performed to detect superimposed acute PE.	109
At least half of thromboembolic events were diagnosed within the first 24 hours of admission and, therefore, not preventable by in-hospital thromboprophylaxis, suggesting that lower threshold of suspicion to perform VTE imaging tests may be reasonable.	36
A baseline chest CT should be considered in all patients with suspected COVID-19 with indication for hospital admission.	37
9. Treatment	
Anticoagulants, antiplatelets and fibrinolytics may all serve potential roles in COVID-19.	49
Anticoagulants, antiplatelets, and fibrinolytics, when used in the right moment, can beneficiate patients suffering from COVID-19.	78
Early anticoagulation may block clotting formation by limiting ongoing fibrin deposition. It reduces microthrombus formation, thereby reducing the risk of major organ damages, specifically ARDS.	44,88
Early anticoagulation treats systemic prothrombotic complications in COVID-19 patients.	44,88
Early anticoagulation gives time for anti-inflammatory agents to work to decrease damage and to allow innate immunity to clear the virus.	44,54,74,88

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Heparins, besides their anticoagulant effects, have also various immunomodulatory properties including protection of glycocalyx from shedding, displaying also an anti-inflammatory action that may be beneficial in COVID-19.	22,39,44,49
Drug-drug interactions between antiplatelet agents and anticoagulants with investigational COVID-19 therapies (mainly antiretroviral drugs, chloroquine and hydroxychloroquine, methylprednisolone) should be considered.	45,53
a. Anticoagulant therapies	
i. Situations to use anticoagulants	
The use of anticoagulants is recommended unless contraindications are present.	17
Anticoagulants appear to be associated to lower mortality in the subpopulation meeting sepsis-induced coagulopathy criteria.	39,46
Anticoagulants appear to be associated to markedly elevated D-dimers.	46-47
It is important to consider the increased risk of death in patients with COVID-19, regarding intubation and other treatments, by increasing the risk of bleeding.	29
The use of anticoagulants may not benefit unselected patients.	32
There seems to be higher mortality among heparin users compared to non-users in patients with D-dimers lower than one upper limit of normal, although the difference was not statistically significant (P=0.26).	32
A risk adapted approach to escalate the dose of anticoagulation should be carefully considered after assessing the bleeding risk for each patient.	54
COVID-19 associated coagulopathy should be managed as it would be for any hospitalized patient, following the established practice of VTE prophylaxis for critically ill patients, and standard supportive care measures for those with SIC or DIC.	53
Anticoagulant effects, both for preventive and therapeutic use, need to be adequately balanced between the potential for reducing thromboembolic events and the increased hemorrhagic risk.	29,53
1. In prophylaxis	
a. Hospitalized patients	
It is important to identify patients who can benefit from anticoagulants.	43
Patients who can benefit from anticoagulants include all patients admitted at ICU.	56,62
The use of LMWH, UFH, or fondaparinux at prophylaxis doses for VTE is strongly recommended for all COVID-19 hospitalized patients.	22,37-46
The use of LMWH, UFH, or fondaparinux at prophylaxis doses for VTE should be maintained 7-14 days after discharge from hospital.	39,45
Prophylaxis and treatment of VTE should be considered to all patients with severe and critical COVID-19.	24,29,48,105
Prophylaxis and treatment of VTE should be considered to those patients with light or moderate forms who do not have contraindications.	42
Prophylaxis and treatment of VTE should be considered to those patients who have a higher estimated risk of thrombosis.	19,29,42,110
Among those patients who have a higher estimated risk of thrombosis, we should consider those who have laboratory tests indicating a hypercoagulability state before progression for consumption coagulopathy.	2,3,66
Strict monitoring is needed for those patients who, among those who have a higher estimated risk of thrombosis, also have laboratory tests indicating a hypercoagulability state before progression for consumption coagulopathy.	66
Thromboprophylaxis should be started irrespectively of risk scores in patients who, among those who have a higher estimated risk of thrombosis, also have laboratory tests indicating a hypercoagulability state before progression for consumption coagulopathy.	37

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Thromboprophylaxis does not seem to have contraindications in patients who, among those who have a higher estimated risk of thrombosis, also have laboratory tests indicating a hypercoagulability state before progression for consumption coagulopathy.	44
A more aggressive individualized strategy might be required in selected cases of patients who, among those who have a higher estimated risk of thrombosis, also have laboratory tests indicating a hypercoagulability state before progression for consumption coagulopathy.	46
Patients with anticoagulant contraindications should be treated with limb compression.	39
Patients with DIC should benefit from standard supportive care measures.	24
Patients with DIC, apart from standard supportive care measures, should benefit from anticoagulation.	43
Patients with sepsis-induced coagulopathy should only receive standard supportive care measures.	24
Scarce evidence is available of the efficacy/safety of heparin and/or antiplatelet agents on sepsis patients.	38-39,43
Regular monitoring of prothrombin time, D-dimers, fibrinogen, platelet count, lactate dehydrogenase, creatinine and alanine aminotransferase (daily or at least 2–3 times per week, depending on the severity of the disease) is suggested for hospitalized patients according to the patients' risk and, therefore, the anticoagulant dosage, should be re-evaluated.	42,45
Concerning prophylactic anticoagulation, antithrombin does not need to be monitored, however this could be considered on an individual basis in cases of DIC, sepsis-induced coagulopathy or heparin resistance.	42
b. Ambulatory patients	
Routine thromboprophylaxis is not recommended in ambulatory patients with acute medical illness or respiratory symptoms, although it has been postulated that the administration of LMWH during the earlier phases of SARS-CoV2 infection may exert a positive effect, not only in terms of thrombosis prevention, but also reducing systemic and pulmonary inflammation, and limiting viral invasion.	36
Ambulatory patients with clinical evidence of vasculitis, or laboratory indicators of progressive inflammation, such as rising IL-6 and/or D-dimer levels should be considered early for anti-inflammatory measures and for full anticoagulation, depending on individual risk versus benefit.	83
2. In treatment	
Data is still limited to suggest the use of full intensity anticoagulation doses as standard treatment, unless otherwise clinically indicated.	24,39,75
Treatment dose of LMWH or fondaparinux may be useful for patients with sepsis associated to COVID-19 in order to reduce inflammatory cytokine potential.	79
Treatment dose of LMWH may be useful for patients with significantly raised D-dimer concentrations to reduce the likeliness of thrombi formation in pulmonary circulation.	22
There are some uncertainties regarding the evidence available on efficacy and safety of treatment dose of LMWH.	39
General COVID-19 patients should be given one to two doses of LMWH daily, until the patient's D-dimer level returns to normal, in order to reduce the coagulation substrate depletion. Considering the difficulties associated to LMWH's management, an initial dose of 1mg/kg q12h intravenously or subcutaneously is recommended only in mild to moderate coagulation dysfunction, with further monitorization according to anti-Xa activity (target range of 0.6~1.0 IU/mL). Furthermore, once FDPs ≥ 10g/mL and/or D-dimers ≥ 5 µg/mL, UFH (3-15 IU/kg per hour) should be used.	17
Early initiation of therapeutic anticoagulation with UFH should be considered prior to significant clinical deterioration to avoid further decline in patients without significant bleeding risks.	111

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
UFH dosage should be determined according to the coagulation function and organ function, in which those with severe coagulation dysfunction may start with a low dose [1 IU/kg per hour] and use laboratory indicators to guide titration. In some specific situations, such as if patients require continuous renal replacement therapy, both UFH/LMWH for systemic anticoagulation or no anticoagulation is recommended and if requiring external membrane oxygenation therapy, UFH is the preferred anticoagulant.	17
If a thrombotic event occurs, therapeutic anticoagulation is indicated.	37,45
If a PE occurs, heparin may be used during hospital stay with transition to a DOAC on discharge.	26,47
When imaging is not feasible, therapeutic-dose anticoagulation may be contemplated if the risk of bleeding is acceptable.	48
If there is high clinical suspicion, therapeutic-dose anticoagulation may be contemplated if the risk of bleeding is acceptable.	29
It might be interesting to determine anti-Xa values at 48 hours after the beginning of anticoagulation, to assure the efficacy of treatment and minimize the hemorrhagic risk.	45
ii. Choice of anticoagulant	
There is very little data on the use of DOAC in COVID-19 patients.	42
There is a successful use of apixaban in PE in COVID-19 patients.	108
Both vitamin K antagonists and DOAC display significant interference with concomitant antiviral (especially anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin) treatment to which these patients are subjected.	39,50
Parenteral anticoagulant drugs seem to be preferred, with choice of drug and dosage depending on the location and severity of the clot.	17
LMWH or UFH, with or without mechanical prophylaxis, are likely to be preferred in general patients and in acutely ill hospitalized ones.	50,77
Regarding the choice of heparin, we cannot be certain about superiority of any of both types.	51
The use of LMWH has been indicated as the best anticoagulant choice for COVID-19 patients.	12,17-18,31,37-38, 64,66,73,94,100
However, other authors state the opposite.	17,38
UFH has a shorter half-life, a convenient monitoring process and that it can be neutralized with protamine, in comparison with LMWH which is not easy to adjust or monitor due to its long half-life.	17
1. UFH	
The UFH recommended dose is 5000 U subcutaneously twice a day.	29
An alternative posology for UFH is 3–15 IU/kg per hour intravenously.	17
In patients with renal failure, it is recommended to administer UFH only once a day, although there is controversial information on the subject.	29,42
In patients under mechanical ventilation who are already heparinized, no additional prevention should be done, due to the risk of bleeding.	29
An increased dose of UFH should be considered in overweight patients (>100 kg), independently of being ventilated or not.	42
The usual procedure to monitor UFH is to use aPTT dosage, keeping the latter's ratio range between 2.0 and 3.0 (i.e. 50-75 seconds).	105
It seems preferable to monitor heparin activity of UFH treatment by other techniques. The most used alternative method is based on anti-Xa levels (with a target value of 0.3-0.7 U/L in all patients with SARS-CoV-2) in general patients.	105
Keeping anti-Xa levels in the therapeutic range seems to be especially important in those patients undergoing extracorporeal membrane oxygenation treatment.	42

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SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Thromboelastography heparinase comparative test has also been recommended to evaluate the coagulation function of severe COVID-19 patients undergoing heparin anticoagulation therapy and to monitor unfractionated heparin dosage.	17
Attention should be given to patients with fluctuations in platelet counts or signs of heparin resistance, because of a possible development of heparin-induced thrombocytopenia.	42
If heparin-induced thrombocytopenia occurs in severe COVID-19 patients, it is recommended the use of the anticoagulant argatroban/bivalirudin.	17
2. LMWH	
a. Prophylactic use	
LMWH is often the chosen agent due to its ease of use, lack of need for laboratory monitoring and familiarity among the spectrum of doctors with varying experience.	51
Together with early intravenous Ig, LMWH is considered to be very important as it may alleviate the hypercoagulable state in patients.	88
i. Action	
The use of LMWH is known to improve the PaO2/FiO2 relation by preventing microthrombi formation and the associated pulmonary coagulopathy, as well as to reduce thrombin production and the likelihood for a VTE.	45
LMWH has anti-inflammatory properties.	45
LMWH anti-inflammatory properties can be explained considering the reduction of concentration of IL-6 and the increase in lymphocytes' count.	72
LMWH anti-inflammatory properties can be explained considering the bidirectional relation between inflammation and thrombosis. Effectively, thrombin blockage induced by LMWH may decrease the inflammatory response and reduce endothelial damage.	45
ii. Dose	
There is no consensus on adequate LMWH doses, and some authors state its use according to the effective thrombotic risk of each individual patient.	52
The recommended doses may vary from 40 to 60mg/day of enoxaparin for at least seven days administered to all patients hospitalized for COVID-19 to 100U/kg (ie, 60-80mg, since 1mg=100U) twice a day, to all patients at the ICU admission.	45,56,62
Unanimity is reached about increased doses of LMWH to be administered to overweight patients with COVID-19.	42,45,62
Recommended doses of LMWH to be administered to overweight patients with COVID-19 are 8000 IU twice daily if body mass index > 35).	62
For patients in intensive care with a large increase in D-dimers, severe inflammation, signs of hepatic or renal dysfunction, imminent respiratory failure, those having multiple risk factors for VTE or having high levels of VWF and factor VIII, intermediate or therapeutic dosing of LMWH or UHF should be considered, according to the bleeding risk.	39,42,45,97
Assessment of the thromboembolic risk and severity of COVID-19 seems to be useful to estimate the need to adjust the dose of LMWH.	45,110
The optimal LMWH regimen is unknown.	56
Demonstration that standard prophylactic doses are sufficient to prevent VTE in COVID-19 patients is lacking.	51
It is probable that higher dosages of LMWH than the standard ones are needed, as demonstrated by thrombotic events (namely PE) in COVID-19 patients despite antithrombotic prophylaxis.	51,56,57
Fibrinogen levels > 700mg/dL + low anti-thrombin levels render COVID-19 patients more resistant to heparin agents.	111

(continued)

SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
At standard prophylactic doses, LMWH does not have a significant impact in the progressive increase in D-dimer levels observed in patients with severe COVID-19.	81
iii. Utility	
A better prognosis is associated to anticoagulation with LMWH in patients having severe COVID-19.	48-49
Anticoagulation with LMWH in patients meeting sepsis-induced coagulopathy (SIC) criteria or with markedly elevated D-dimers is associated to a better prognosis.	32
Patients meeting SIC criteria or with markedly elevated D-dimers had a significant reduction in mortality (up to 37% reduction of 28-day mortality).	49
A significant reduction in mortality was observed both in general ARDS with LMWH administration during the initial first week of onset and in patients having severe COVID-19 or those with D-dimers greater than six times the upper limit of normal.	17,45,64
Prophylactic LMWH is an unconvincing strategy to treat severe COVID-19 coagulopathy due to DIC.	111
COVID-19 patients on prophylactic dose of LMWH do not typically develop overt DIC but, in the rare cases where it does develop, it tends to be restricted to late-stage disease.	81
LMWH is an adequate strategy to prevent the development of DIC.	81,111
b. Therapeutic use	
When used therapeutically, enoxaparin should be administered in the dose of 10mg/10kg every 12 hours subcutaneously, adjusted according to renal function, age, and hemorrhagic risk.	60-61
When used therapeutically, enoxaparin is considered a safe therapy and no severe bleeding was reported.	78
i. Dose	
The answer to the question of whether therapeutic doses of either UFH or LMWH should be considered for all patients is currently unknown and the authors would currently reserve such a dose for those who have confirmed thrombosis including filter thrombosis.	51
The use of anticoagulant therapy resulted in lower DIC score in COVID-19 patients.	78
The use of anticoagulant therapy resulted in lower mortality in patients with sepsis-induced coagulopathy score ≥ 4 (LMWH: 40.0% *vs* No-LMWH: 64.2%, *P*=0.03), lower mortality in patients with D-dimers over six-fold the upper limit of normal (LMWH: 32.8% *vs* No-LMWH: 52.4%, *P*=0.02), but there was no overall benefit for patients on LMWH (LMWH: 30.3% *vs* No-LMWH: 29.7%, respectively, *P*=0.91).	32
ii. Utility	
Although anticoagulation therapy does not seem to improve the clinical situation of critical patients with thromboembolic events, it gives time for the primary disease to get better, postponing or blocking its progression and, consequently, improving its prognosis.	78
In advanced COVID-19, systemic heparin will not breakdown the existing clot, but reduces microthrombi in a certain extent.	80,111
iii. Antiplatelet therapies	
There is very little data on the use of antiplatelet agents.	39
Even though antiplatelet agents do not seem to be first line choice either in anticoagulation prophylaxis or therapy, they may play a role in COVID-19.	62-63
Thrombocytosis in the context of SARS-CoV-2 infection can benefit from antiplatelet agents.	62-63
Clopidogrel has been used in COVID-19 patients in the posology of 300mg loading dose followed by 75mg/day if platelet count > 400.000 cells/iL.	62
Clopidogrel has been used in COVID-19 patients associated or not to heparin.	63
Dipyridamole, because of its antiviral and antioxidant properties, has beneficial effects in patients with COVID-19.	39

(continued)

SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Although less likely to influence coagulation events, PAR-1 antagonists (developed as antiplatelet drugs for the treatment of cardiovascular disease) might potentially attenuate the deleterious effects associated to activation of the coagulation cascade and thrombin formation.	22
A clinically approved PAR-1 antagonist was shown to reduce levels of proinflammatory cytokines, neutrophilic lung inflammation, and alveolar leak during bacterial pneumonia and lipopolysaccharide--induced lung injury in murine models.	22
The use of glycoprotein IIb/IIIa inhibitors may also be considered in every ST-elevation myocardial infarction patient with COVID-19 to prevent the risk of acute stent thrombosis.	112
No good evidence is available on the efficacy and safety of antiplatelet agents on sepsis patients.	39
iv. Other therapies	
1. Nafamostat	
The use of nafamostat, a fast-acting proteolytic inhibitor of the transformation of fibrinogen into fibrin, proved that it may be effective against COVID-19 from both 'anti-viral' and 'anti-DIC with enhanced fibrinolysis' perspective. Its disadvantage is that it has weaker anticoagulation actions compared with its antifibrinolytic actions but its combination with heparin may compensate for this weakness and further augment the positive effects.	113
2. Fibrinolytic agents	
The use of anticoagulants and fibrinolytics in COVID-19 requires further study, including identification of components most deranged to enable effective targeted therapy.	49,100
3. Anti-thrombin supplementation	
Even though at first sight it may seem incongruent, anti-thrombin supplementation may also be of utility for COVID-19 patients.	111
4. tPA	
In advanced COVID-19, salvage therapy with tPA to restore microvascular patency may play a role.	111
By re-addressing the fibrinolytic balance, administration of tPA to ARDS patients may confer anti-inflammatory effects.	44
The recommended therapy in advanced COVID-19 seems to be a combination of intravenous tPA with heparin perfusion.	100
To prevent recurrence of the suspected pulmonary microvascular thrombosis underlying COVID-19 ARDS, larger bolus-dose tPA (50mg or 100mg bolus) without holding anticoagulation should be considered.	100
While the mortality in COVID-19 ARDS is exceptionally high, the risks of tPA must still be carefully considered given the approximate 1% risk of catastrophic bleeding from tPA in non-stroke patients.	100
5. Fibrinogen transfusion	
The possibility of performing a fibrinogen transfusion (that, in a medical DIC setting, the European trauma guidelines on management of bleeding and coagulopathy recommend being triggered at < 1.5g/l - grade of evidence 'low level') may pose some concerns.	113
One concern posed by the possibility of performing a fibrinogen transfusion to COVID-19 patients is related to the recommendation to administer blood products to patients who have deranged coagulation but are not bleeding.	113
Apart from its potential for harm, fibrinogen transfusion in COVID-19 patients who are not bleeding can eventually be considered as an overtreatment, with its adverse economic and resource implications.	113
Although, justification has been given as to why fibrinogen transfusion ought now to be widened to include nonbleeding patients, it may be more advisable to administer thromboprophylaxis to patients according to current thromboprophylaxis guidance based on clinical factors.	25

(continued)

SUPPLEMENTARY TABLE 1. Synthesis of results *(continued)*

Statement	References
Another concern posed by the possibility of performing a fibrinogen transfusion to COVID-19 patients is evidenced by the fact that it seems odd to recommend LMWH to reduce thrombotic risk while also recommending fibrinogen supplementation in the absence of bleeding, despite the risk of provoking thrombosis.	25
6. Anti-hemorrhagic agents	
As far as active bleeding is concerned, if hemorrhage is not effectively stopped in COVID-19 patients after active replacement therapy, recombinant factor VII is recommended.	17
7. Local citrate	
In COVID-19 patients who require continuous renal replacement therapy, treatment with local citrate anticoagulation should be used, to avoid aggravating coagulation disorders.	17
8. Primary coronary angioplasty	
Other kinds of therapies have also been essayed in COVID-19 patients such as the promotion of primary coronary angioplasty as the first-choice revascularization technique and the use of new generation P2Y12 inhibitors.	112
9. Immunoglobulins	
The use of intravenous Ig may provide COVID-19 patients with effective clinical benefits and inhibit the formation of inflammatory factors storm ('cytokine storm').	88

* Notes: LE = Level of evidence; SC = Strength of recommendation; COVID-19 = Coronavirus disease of 2019; VTE = Venous thromboembolism; PE = Pulmonary embolism; IS = Ischemic stroke; ACS = Acute coronary syndrome; DIC = Disseminated intravascular coagulation; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; CI = Confidence interval; ICU = Intensive care unit; MOF = Multiorgan failure; ISTH = International Society of Thrombosis and Haemostasis; PT = Prothrombin time; PAR = Proteinase-activated receptor; IL-6 = Interleukin-6; aPTT = Activated partial thromboplastin time; CT = Computed-tomography; ARDS = Acute respiratory distress syndrome; FDP = Fibrinogen degradation products; VWF = Von Willebrand factor; CWA = Clot waveform analysis; Ig = Immunoglobulin; SIC = Sepsis-induced coagulopathy; LMWH = Low-molecular weight heparin; UFH = Unfractionated heparin; DOAC = Direct oral anticoagulant; tPA = Tissue plasminogen activator.

APPENDIX 1
Search queries according to database

MEDLINE®
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND ((clot*) OR (thrombo*) OR (*coagul*) OR (emboli*) OR (*aggregat*) OR (purpur*) OR (ecchymosis))

Web of Science®
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND ((clot*) OR (thrombo*) OR (*coagul*) OR (emboli*) OR (*aggregat*) OR (purpur*) OR (ecchymosis))

SciELO®
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (clot*)
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (thrombo*)
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (*coagul*)
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (emboli*)
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (*aggregat*)
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (purpur*)
((sars-cov-2) OR (n-COV) OR (COVID-19) OR ("New coronavirus") OR ("Novel coronavirus")) AND (ecchymosis)

APPENDIX 2
SORT Taxonomy

Level of evidence
Level 1 – Good quality patient-oriented evidence.
Level 2 – Limited-quality patient-oriented evidence.
Level 3 – Other evidence.