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COVID-19 associated coagulopathy and inflammatory response: what do we know already and what are the knowledge gaps?

Short Title: COVID-19 associated coagulopathy knowledge gaps

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Abstract

Patients with COVID-19 frequently experience a coagulopathy associated with a high incidence of thrombotic events leading to poor outcomes. Here, biomarkers of coagulation (such as D-dimer, fibrinogen, platelet count), inflammation (such as interleukin-6) and immunity (such as lymphocyte count) as well as clinical scoring systems (such as SOFA, ISTH DIC and SIC score) can be helpful in predicting clinical course, need for hospital resources (such as ICU beds, intubation and ventilator therapy, and ECMO) and patient's outcome in patients with COVID-19. However, therapeutic options are actually limited to unspecific supportive therapy. Whether viscoelastic testing can provide additional value in predicting clinical course, need for hospital resources and patient's outcome or in guiding anticoagulation in COVID-19 associated coagulopathy is still incompletely understood and currently under investigation (e.g., in the ROHOCO study). This paper summarizes what we know already about COVID-19 associated coagulopathy and – perhaps even more importantly – characterizes important knowledge gaps.

Key Words: Anticoagulation, coagulopathy, COVID-19, SARS-CoV-2, thrombosis.

Glossary of Terms

A5	Amplitude of clot firmness 5 minutes after CT
A10	Amplitude of clot firmness 10 minutes after CT
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence interval
cfDNA	Cell-free deoxyribonucleic acid
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Coagulation time
DAMPs	Damage-associated molecular patterns
DIC	Disseminated intravascular coagulation
DOACs	Direct oral anticoagulants
ECMO	Extracorporeal membrane oxygenation
exRNA	Extracellular ribonucleic acid
EXTEM	Thromboelastometry assay with extrinsic activation
FIBTEM	Thromboelastometry assay to assess fibrin contribution to clot firmness
HR	Hazard ratio
ICU	Intensive care unit
IL-6	Interleukin-6
INR	International normalized ratio
IQR	Interquartile range
ISTH	International society on thrombosis and hemostasis
LDH	Lactate dehydrogenase
LI60	Lysis index 60 minutes after CT
LMWH	Low molecular weight heparin

LY30	Lysis 30 minutes after MA
MA	Maximum amplitude of clot firmness
MCF	Maximum clot firmness
MERS-CoV	Middle East respiratory syndrome coronavirus
ML	Maximum lysis
MOF	Multiple organ failure
NETs	Neutrophil extracellular traps
NF-kappaB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor type 1
PAMPs	pathogen-associated molecular patterns
PE	Pulmonary embolism
PRRs	Pattern recognition receptors
ROHOCO	ROTEM analysis and standard coagulation tests in hospitalized patients with COVID-19
ROTEM	Rotational thromboelastometry
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SIC	Sepsis-induced coagulopathy
SIRS	Systemic inflammatory response syndrome
SNPs	Single nucleotide polymorphisms
SOFA	Sequential organ failure assessment
TEG	Thromboelastography
TF	Tissue factor

TLRs	Toll-like receptors
TMPRSS2	Transmembrane protease serine subtype 2
tPA	Tissue plasminogen activator
UFH	Unfractionated heparin
VET	Viscoelastic testing
VTE	Venous thromboembolism
WHO	World health organization

Introduction

After severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, H_1N_1 influenza in 2009 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, the SARS-CoV-2 pandemic is now challenging the world with COVID-19. Although most of the infected persons either have sub-clinical or mild clinical symptoms, a small patient population has severe disease manifestations of COVID-19. In particular, this applies for male patients older than 60 years and patients with comorbidities. Patients with poor outcome are characterized by a high incidence of COVID-19 associated coagulopathy, venous thrombosis, pulmonary embolism/thrombosis, and multiple organ failure.[1]

What do we know already about COVID-19-associated coagulopathy?

COVID-19 is associated with a high incidence of venous thrombosis and pulmonary embolism/thrombosis

Cui et al. reported an incidence of venous thromboembolism (VTE) of 25% (20/81) in critically ill patients with COVID-19 treated at the intensive care unit (ICU) which was at least two-times higher compared to other critically ill patients.[2,3] Mortality in these patients was 40%. A D-dimer cutoff of ≥ 1.5 µg/mL (reference range < 0.5 µg/mL) predicted VTE with a sensitivity of 85.0%, a specificity of 88.5% and a negative predictive value of 94.7%. A high incidence of VTE of 31% in 184 critically ill COVID-19 patients despite pharmacologic thromboprophylaxis was confirmed by Klok et al.[4] Here, pulmonary embolism (PE) was with 81% the most frequent thrombotic complication. Llitjos et al. reported that VTE was even detected in 100% (8/8) of severe COVID-19 patients treated with prophylactic and in 56% (10/18) in patients with therapeutic anticoagulation.[5] Even if VTE was observed most often in ICU patients,[6] Lodigiani demonstrated that half of the VTE (overall 21%) were diagnosed already within 24 hours of hospital admission.[7] Therefore, monitoring should be initiated early after hospital admission and should not be limited on critically ill COVID-19 patients treated at the ICU. However, COVID-19 patients receiving continuous renal replacement therapy or

extracorporeal membrane oxygenation (ECMO) may even be at increased risk of VTE, PE and circuit clotting.[8] Finally, Wichmann et al. detected VTE in 58% (7/12) of autopsies in COVID-19 patients and PE was the direct cause of death in 33% (4/12).[9] This high incidence of pulmonary thrombosis and embolism in autopsies has recently been confirmed by other authors.[10,11]

Biomarkers can help predict the clinical course of COVID-19 patients

Gao et al. reported that D-dimer differentiated between COVID-19 patients with severe versus mild disease. The optimal threshold and area under the ROC curve of D-Dimer were 0.280 µg/mL and 0.750, respectively.[12] Zhou et al. showed in their multivariable regression increasing odds of in-hospital death associated with older age (OR, 1.10, 95% CI, 1.03-1.17, per year increase; P = 0.0043), and D-dimer greater than 1 µg/mL (OR, 18.42, 95% CI, 2.64-128.55; P = 0.0033) on hospital admission.[13] Zhang et al. reported an optimum cutoff value of D-dimer of ≥ 2.0 µg/mL within 24 hours after hospital admission to predict in-hospital mortality with a sensitivity of 92.3% and a specificity of 83.3% and a hazard ratio of 51.5 (95% CI, 12.9-206.7).[14] Accordingly, the potential risk factors of older age and D-dimer ≥ 2 µg/mL may help clinicians to identify patients with poor prognosis at an early stage. Elevated D-dimers as a risk factor for Acute Respiratory Distress Syndrome (ARDS) and mortality have been confirmed by Tang et al. and Wu et al.[15,16] Since most patients with severe COVID-19 are older than 60 years, it seems to be reasonable to use an age-adjusted D-dimer cut off value (patient's age x 10 µg/L).[17-19] Notably, Tang et al. reported that patients with D-dimer > 3 µg/mL (6fold of upper limit of normal) showed a significant reduction in 28-day mortality (32.8% vs. 52.4%; P = 0.017) if treated with unfractionated heparin (UFH) or low molecular weight heparin (LMWH).[20-22] Accordingly, D-dimer may be considered as a good biomarker for severe COVID-19 infection and the need for intensified (intermediate or therapeutic dose) and extended (to post hospital discharge) thromboprophylaxis, even though there is still no clear evidence available.[23.24]

Gao et al. reported that also IL-6 plasma concentration (reference range < 7 pg/mL) differentiated between mild and severe groups of COVID-19 patients. The optimal threshold and area under the ROC curve of IL-6 were 24.3 pg/mL and 0.795, respectively.[11] Notably, the area under the ROC curve of IL-6 combined with D-dimer was 0.840. The specificity of predicting the severity of COVID-19 by IL-6 and D-dimer tandem testing was up to 93.3%, while the sensitivity of IL-6 and D-dimer by parallel test in the severe COVID-19 was 96.4%. Accordingly, the combined d-dimer and IL-6 testing provides the highest sensitivity and specificity for early prediction of COVID-19 severity. The prognostic value of IL-6 has been confirmed by Ruan et al. who demonstrated that non-survivors had 1.7-times higher IL-6 values compared to survivors.[25] Accordingly, Henry recommended tracking IL-6 before and during ECMO since patients with hyper-inflammation might not benefit but rather be harmed by ECMO therapy.[26] Furthermore, IL-6 plasma concentrations are consistently elevated and inversely correlated with survival in children and adults during ECMO.[27]

Lymphopenia (lymphocyte count; median (IQR), 800 (600-1100) /µL; reference range, 1100-3200/µL) has been reported in 70.3% of hospitalized COVID-19 patients.[28] Also lymphocyte count - as a biomarker of an exhausted adaptive immune system – is associated with COVID-19 severity. Patients who died from COVID-19 are reported to have had significantly lower lymphocyte counts than survivors.[26] Tracking both lymphocyte count and IL-6 may reflect the balance between the innate and adaptive immune system in patients with severe COVID-19.

Clinical scores such as SOFA, SIC and ISTH DIC score predict mortality in COVID-19

Zhou et al. showed in their multivariable regression increasing odds of in-hospital death associated with older age (OR, 1.10, 95% CI, 1.03-1.17, per year increase; P = 0.0043), and higher Sequential Organ Failure Assessment (SOFA) score (OR, 5.65, 95% CI, 2.61-12.23; P < 0.0001). In combination with D-dimer > 1 µg/mL this can help clinicians to identify COVID-19 patients with poor prognosis at an early stage.[13] SOFA score as a part of the Sepsis-induced Coagulopathy (SIC) score can also identify COVID-19 patients which might benefit from

intensified thromboprophylaxis. Here, Tang et al. reported that patients with SIC score ≥ 4 or D-dimer > 3 µg/mL (6fold of upper limit of normal) showed a significant reduction in 28-day mortality (40.0% vs. 64.2%, P = 0.029 and 32.8% vs. 52.4%; P = 0.017, respectively) if treated with UFH or LMWH.[20-22] Furthermore, 71.4% of COVID-19 non-survivors and 0.6% survivors met the ISTH DIC criteria during their hospital stay.[15] Therefore, clinical scoring systems such as SOFA, SIC and ISTH DIC score can be helpful in predicting outcome in patients with COVID-19. However, clinical scores such as the ISTH DIC score have to be interpreted in the clinical context and as a dynamic process. Accordingly, not every patient with a DIC score ≥ 5 is suffering definitively from overt DIC.

What are the knowledge gaps?

Is COVID-19 associated coagulopathy different from sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC)?

Tang et al. reported that 71.4% of patients who die of COVID-19 are meeting ISTH criteria for disseminated intravascular coagulopathy (DIC) while only 0.6% of patients who survived meet these criteria.[15,29] However, COVID-19 is characterized as a predominantly pro-thrombotic disease with elevated D-dimers (>1 µg/mL; OR, 18.42; 95% CI, 2.64-128.55; P=0.0033), higher Sequential Organ Failure Assessment (SOFA) score (OR, 5.65; 95% CI 2.61-12.23; P<0.0001), high fibrinogen levels (median (IQR), 4.55 (3.66-5.17) g/L; reference range, 2.0-4.0 g/L), but only mildly decreased antithrombin levels (median (IQR), 91 (83-97)%; reference range, 80-120%) on ICU admission and microvascular thrombosis rather than a bleeding diathesis.[12-16,30,31] However, pathophysiology of COVID-19-associated coagulopathy seems to be different from SIC and DIC caused by other infectious diseases.[32-34]

What are the differences between viral and bacterial sepsis-induced coagulopathy?

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase

in the SOFA score of 2 points or more, which is associated with an in-hospital mortality greater than 10%.[35] Early phase of bacterial sepsis is characterized by hypercoagulability due to tissue factor expression on circulating monocytes and micro-particles, increased fibrinogen plasma concentration, platelet activation and subsequent dysfunction, and hypofibrinolysis/fibrinolysis shutdown.[36,37] Tissue factor expression on circulating monocytes and micro-particles is triggered by bacterial toxins (lipopolysaccharides) and other pathogen-associated molecular patterns (PAMPs) via NF-kappaB1 activation and subsequent induction of plasminogen activator inhibitor type 1 (PAI-1) and pro-inflammatory cytokines such as interleukin-6 (IL-6) (**Figure 1**).[38-40] Tissue factor expression on circulating cells and micro-particles, changes in clot firmness and hypofibrinolysis can be detected by thromboelastometry (**Figure 2**).[41,42] On the one hand, this allows for discrimination between Systemic Inflammatory Response Syndrome (SIRS) and bacterial sepsis, and on the other hand, for prediction of mortality in sepsis.[43-46] Furthermore, both cell-free DNA (cfDNA) and extracellular RNA (exRNA) are activating coagulation in sepsis. While higher exRNA levels correlated with a faster coagulation time (CT) and more stable clots (MCF), cfDNA correlated with a shorter CT but also less fibrinolysis (LI60) in thromboelastometry.[47] Zuo et al. reported recently that neutrophil extracellular traps (NETs), including cell-free DNA, are elevated in severe COVID-19 patients receiving mechanical ventilation and strongly correlate with acute phase reactants, including CRP, D-dimer and LDH. These NETs have the potential to propagate inflammation and microvascular thrombosis.[48] Whether extracellular RNA derived from SARS-CoV-2 contributes to the hypercoagulability seen in COVID-19 is not known. However, RNAemia is detected only in critically ill COVID-19 patients and is closely correlated with very high IL-6 levels ($\geq$ 100 pg/mL; r = 0.902) and poor prognosis.[49] In contrast to COVID-19, patients present with decreased plasma fibrinogen concentrations in some viral infections – in particular in hemorrhagic fevers such as Ebola or Dengue.[50-53] Accordingly, viral infection does not change

hemostasis in an uniform way. Dependent on the pathogen, it can result in hypo- or hypercoagulability with the clinical appearance of bleeding or thrombosis.

What is the role of the innate and adaptive immune system in COVID-19?

The innate immune system is based on physical (e.g., epidermis and ciliated respiratory epithelium) and chemical (e.g., gastric acid) barriers to infection, as well as on different cell types recognizing invading pathogens and activating antimicrobial immune response (dendritic cells, macrophages and granulocytes). It constitutes the first line of host defense during infection and therefore plays a crucial role in the early recognition and subsequent triggering of a pro-inflammatory response to invading pathogens. The innate immune response is relatively nonspecific and relies on recognition of evolutionarily conserved structures on pathogens, termed pathogen-associated molecular patterns (PAMPs), through a limited number of pattern recognition receptors (PRRs; e.g., Toll-like receptors (TLRs)). In contrast, the adaptive immune system is responsible for the elimination of pathogens in the late phase of infection and in the generation of immunological memory. It is characterized by specificity developed by clonal gene rearrangements from a broad repertoire of antigen-specific receptors on lymphocytes. If the adaptive immune system is not able to clear the viruses, pro-inflammatory cytokines – in particular IL-6 – can cause host damage by triggering a vicious circle of systemic inflammatory response including pneumonia.[54] The release of damage-associated molecular patterns (DAMPs) from the damaged tissues and cells can further stimulate PRR signaling and lead to a chain reaction culminating in viral sepsis if the infection is not cleared. This 'cytokine storm' can result in multiple organ failure and death.[25,55]

Which patient will benefit from anti-inflammatory drugs in COVID-19?

General treatment with corticosteroids is not recommended in COVID-19 since it may delay virus clearance and promote superinfection.[56] However, some authors recommend dexamethasone 20 mg/day for 5 days and then 10 mg/day for 5 days in patients with ARDS within 24 hours after ARDS diagnosis.[28,57] The indication must be discussed with the ICU team.

Russell et al. found no published evidence for or against the use of NSAIDs in COVID-19 patients. Meanwhile, there appeared to be some evidence that corticosteroids may be beneficial if utilized in the early acute phase of infection, however, conflicting evidence from the World Health Organization (WHO) surrounding corticosteroid use in certain viral infections means this evidence is not conclusive.[58] Patients with ARDS and high IL-6 levels may benefit from tocilizumab, a monoclonal antibody targeting the IL-6 receptor, indicated in cytokine release syndrome (CRS).[59] Several studies on the efficacy and safety of corticosteroids and tocilizumab in COVID-19 are running, actually (NCT04273321, NCT04325061, NCT04343729, NCT04306705, NCT04317092, NCT04320615, NCT04322773, NCT04332913).

What patient demographics affect the incidence of thrombosis in COVID-19 patients?

Ethnicity has major effects on thrombotic risk, with a 3-4-fold lower risk in Chinese compared to Caucasians and a significantly higher risk in African-Americans.[60] Accordingly, Fox et al. reported autopsy finding of thrombosis and microangiopathy in the small vessels and capillaries of the lung that significantly contributed to death in African American patients with COVID-19 from New Orleans.[61] However, it is still under debate how much social factor contribute to the increased mortality in African American patients with COVID-19.[62] Furthermore, gene polymorphisms such as the PAI-1 polymorphism, the NF-kappaB1 promoter polymorphism and several cytokine gene polymorphisms have been show to impact complications and mortality in bacterial sepsis.[63-67]

Older age is a risk factors associated with the development of ARDS and progression from ARDS to death in COVID-19 (hazard ratio [HR], 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67, respectively).[14] Despite an increasing number of case reports dealing with COVID-19-associated deaths in younger patients, older age has been confirmed as one of the most important risk factors for COVID-19-associated mortality in recent publications.[68,69] There are many reasons for this increased mortality in patients older than 60 years including a higher likelihood of co-morbidities (diabetes, obesity, chronic obstructive pulmonary disease,

chronic heart disease, chronic renal disease, thrombosis), decreased organ function reserves, prolonged hospitalization times, generally weaker immune response (immunosensescence), and chronic inflammatory diseases. Older adults also experience persistent T cell exhaustion in part due to constant low-level inflammation, thought to be caused by accumulation of self-debris brought on by a decrease in the ability to clear them. This process, often called "inflammaging" is characterized by elevated baseline levels of the cytokines IL-6, IL-1, and TNF-alpha.[70-71] About 60% of COVID-19 patients are male.[72] Notably, transmembrane protease serine subtype 2 (TMPRSS2) is both the most frequently altered gene in primary prostate cancer and a critical factor enabling cellular infection by coronaviruses, including SARS-CoV-2. The modulation of its expression by sex steroids could contribute to the male predominance of severe infections and given that TMPRSS2 has no known indispensable functions, and inhibitors (e.g., camostat) are available, it is an appealing target for prevention or treatment of respiratory viral infections.[73] Two studies on the efficacy and safety of camostat therapy alone or in combination with hydroxychloroquine in COVID-19 are running, actually (NCT04321096 and NCT04338906).

What viscoelastic parameters may be helpful in guiding therapy in patients with COVID-19?

On the one hand, hypofibrinolysis/fibrinolysis shutdown (lysis index 60 min after CT; LI60 ≥ 96.5%) and hypocoagulability (decreased maximum clot firmness; MCF ≤ 55 mm) in thromboelastometry have been shown to predict increased mortality in bacterial sepsis.[43-46] Furthermore, early platelet dysfunction predicts mortality in bacterial sepsis.[37] Whether this applies for COVID-19 associated coagulopathy, too, is actually under clinical investigation. On the other hand, increased clot firmness amplitudes (A10 > 61.5 mm or MCF/MA > 68 mm and FIBTEM MCF > 25 mm) in thromboelastometry/graphy have been shown to be predictive for thrombosis in adults and neonates undergoing cardiac and non-cardiac surgery (**Figure 2**).[74-78]

Recently, first studies confirmed markedly hypercoagulable viscoelastic profiles characterized by increased clot firmness parameter (A5, A10, MCF or MA) in patients with COVID-19. Here, Almskog et al. showed in their study including 60 COVID-19 patients and 76 healthy subjects that thromboelastometry maximum clot firmness at hospital admission predicts the final level of care (regular ward or ward with specialized ventilation support).[79] Patients who needed transfer to specialized wards showed already a more hypercoagulative state at hospital admission compared to patients who could be managed at the normal ward and did not require intubation and mechanical ventilation (EXTEM MCF, 76 vs. 70 mm; P<0.01 (reference range, 50-72 mm) and FIBTEM MCF 33 vs. 27 mm; P=0.04 (reference range, 9-25 mm)). Whether early thromboelastometry analysis at hospital admission can predict outcome (thrombosis and mortality) in COVID-19 will be analyzed at a later stage of this research project. Another prospective, multicenter (22), multinational (11) observational study on the predictive value of ROTEM analysis and standard coagulation tests in (500) hospitalized patients with COVID-19 (ROHOCO Study) is currently recruiting patients.

Mortus et al. assessed hemostasis in 21 critically ill COVID-19 patients with 19% requiring ECMO support and 86% requiring renal replacement therapy.[80] All patients received deep vein thrombosis chemoprophylaxis on ICU admission and therapeutic anticoagulation (UFH or LMWH) for thrombotic complications. There were no statistically significant differences in prothrombin time, INR, partial thromboplastin time, or platelet levels between 10 patients with at least two thrombotic events vs 11 patients with fewer than two events. In contrast, innate TEG MA was significantly greater for the high event rate group than the low event rate group (mean [SD], 75 [7] mm vs. 61 [21] mm; P = 0.01). Elevated MA (> 65 mm) was observed in 100% in the high event rate group vs 45% in the low event rate group. Innate TEG MA provided 100% sensitivity and 100% negative predictive value for multiple thromboembolic events. LY30 was decreased to 0.5% in the high event rate group.

Pavoni et al. demonstrated in 40 critically ill patients with COVID-19 that hypercoagulability in thromboelastometry persists in the first five days but it deceases ten days after, without returning to normal values.[81] Antithrombin levels and platelet count did not decreased in these patients, but fibrinogen, FIBTEM MCF and IL-6 levels decrease in parallel during recovery (**Figure 1**). The good correlation between fibrinogen and IL-6 ($r = 0.711$; $P = 0.003$) and the procoagulant viscoelastic pattern in COVID-19 patients with acute respiratory distress syndrome was also confirmed by Ranucci et al.[82] Accordingly, plasma fibrinogen concentration or FIBTEM MCF might be used as a surrogate for IL-6 when this test is not 24/7 or timely available.

Spiezia et al. confirmed that COVID-19 patients admitted to the ICU for acute respiratory failure present a severe hypercoagulability (EXTEM MCF, 69 ± 6 mm vs. 64 ± 5 mm; $P = 0.0003$ and FIBTEM MCF, 31 ± 9 mm vs. 18 ± 6 mm; $P < 0.0001$) rather than a consumptive coagulopathy (no significantly decreased antithrombin level or platelet count) when compared to healthy controls.[34] Panigada et al. reported the same observation that their thromboelastography results in critically ill COVID-19 patients support hypercoagulability together with a severe inflammatory state but are not consistent with acute DIC.[83] Here, besides fibrinogen, coagulation factor VIII and von Willebrand factor antigen are increased as typical acute phase reactants to 140-380%, 300-400% and 200-500%, respectively.

Madathil et al. reported that critically ill COVID-19 patients receiving mechanical lung ventilation (and 27% additional ECMO support) presented fibrinolysis shutdown with 0% maximum lysis in EXTEM and FIBTEM despite high CRP and D-dimers.[84] Accordingly, Wright et al. showed that fibrinolysis shutdown correlates to thromboembolic events and renal failure in severe COVID-19 infection.[85] Here, the best predictive value was provided by the combination of elevated D-dimer (>2.6 µg/mL) and fibrinolysis shutdown (TEG LY30 = 0%).

In patients presenting neither elevated D-dimer nor fibrinolysis shutdown, the incidence of venous thromboembolism was 0% and for renal failure with the need for dialysis 14%. In contrast, in patients presenting elevated D-dimer and fibrinolysis shutdown, the incidence of venous thromboembolism was 50% and for renal failure with the need for dialysis 80%.

Accordingly, thrombolytic therapy might be reasonable, in particular in patients with sudden deterioration of oxygenation and signs of pulmonary hypertension and right ventricular failure.[86] Actually, the value of thrombolytic therapy with tissue plasminogen activator (tPA) is under clinical investigation (NCT04356833, NCT04357730).[29,87] Notably, a FIBTEM MCF cutoff < 13 mm provides a sensitivity of 94% and a specificity of 80% to predict bleeding complications in patients with acute ischemic stroke undergoing thrombolytic therapy with tPA.[88] This might help selecting the right patients for thrombolytic therapy.

Furthermore, Maier et al. as well as Ranucci pointed out that anticoagulation with direct thrombin inhibitors (argatroban or bivalirudin) in COVID-19 patients with suspected heparin-induced thrombocytopenia or heparin resistance can result in falsely low results for plasma fibrinogen using the Clauss method (e.g., 99 mg/dL instead of 590 mg/dL).[89,90] In contrast, FIBTEM and TEG Functional Fibrinogen measurements still provide reliable clot firmness results under direct thrombin inhibitor therapy.

Accordingly, Rubulo et al. advised the use of viscoelastic point-of-care testing for all COVID-19 patients with severe pneumonia in their paper "technologies to optimize care of severe COVID-19 patients for healthcare providers challenged by limited resources".[91] Also the Chinese Society on Thrombosis and Haemostasis recommends to use viscoelastic testing in COVID-9 patients with coagulopathy to monitor hemostasis and anticoagulation in particular in patients requiring ECMO, in patients with heparin-induced thrombocytopenia requiring alternative anticoagulation, and in patients with bleeding complications requiring goal-directed replacement therapy.[92] However, further data are needed to define the role of viscoelastic testing in the management of patients with thrombo-inflammation and severe COVID-19.[93]

Which (if any) patient with COVID-19 has an increased bleeding risk?

In contrast to viral hemorrhagic fever such as Dengue, there is only one report regarding hemorrhagic problem in patients with COVID-19. Here, Joob et al. presented observations from Thailand with 1 out of 41 COVID-19 patients presented mild bleeding (petechiae).[94] Tang et al. reported that 57.1% of the non-survivors exhibited thrombocytopenia (33.3% had 50-100 platelets/nL and 23.8% had <50 platelets/nL).[15] Accordingly, thrombocytopenia is a marker of severe disease and a prognostic marker of mortality in patients with COVID-19, and thus can serve as a clinical indicator of worsening illness during hospitalization.[95] While thrombocytopenia is a key diagnostic component in DIC, the data from COVID-19 studies raises the questions of whether thrombocytopenia in COVID-19 is a part of sepsis-induced DIC and/or a direct platelet-viral interaction and if so, is this interaction beneficial for the host or for the virus, and what are the possible mechanisms? These questions are worth exploring further in clinical studies. Several COVID-19 patients even present thrombocytosis.[83] Studies assessing platelet function on the one hand and the effect of antiplatelet drugs on outcome in COVID-19 patients on the other hand are actually under clinical investigation (NCT04365309, NCT04368377).[96]

However, restricted platelet transfusion has been shown to be associated with a significant lower mortality compared to liberal platelet transfusion in several settings.[97-99] Furthermore, platelet transfusion might increase the proinflammatory response as well as the risk of VTE and PE in COVID-19.[99-100] Therefore, platelet transfusion should be considered carefully in COVID-19 patients.

What is the ideal anticoagulation strategy for patients with COVID-19?

Due to the high incidence of VTE and PE, thromboprophylaxis is recommended in all hospitalized COVID-19 patients and should also be maintained for 7-14 days at home after hospital discharge in case of pre-existing or persisting VTE risk factors.[23,24] However, the optimal drug and dose for thromboprophylaxis in COVID-19 patients is actually unknown.

LMWH or UFH is used in most centers.[17,18] Since several patients with severe COVID-19 develop hypercoagulability with increased D-dimer and fibrinogen levels but only moderately decreased antithrombin levels, as well as VTE and PE even under thromboprophylaxis, some patients might benefit from intermediate-dose or therapeutic anticoagulation.[5,6,12-18,22,29-31,101] Tang et al. reported that patients with SIC score ≥ 4 or D-dimer > 3 µg/mL (6fold of upper limit of normal) showed a significant reduction in 28-day mortality (40.0% vs.64.2%, P = 0.029 and 32.8% vs. 52.4%; P = 0.017, respectively) if treated with UFH or LMWH. No difference in 28-day mortality was found between heparin users and nonusers in the overall population of severe COVID-19 patients (30.3% vs. 29.7%, P = 0.910). Thromboprophylaxis was done by administering LMWH (40-60 mg enoxaparin/day) or UFH (10,000-15,000 U/day) for at least 7 days.[20,21]

Notably, DOAC patients treated with antiviral drugs show an alarming increase in DOAC plasma levels.[24,102] Therefore, some authors recommend replacing DOACs by UFH or LMWH as long as antiviral therapy is necessary.[24,102] Here, thromboelastometry can be helpful to detect supra-therapeutic DOAC levels in a timely manner.[103,104] Furthermore, it is not known, whether supplementation of antithrombin and/or thrombomodulin is helpful due to their anticoagulant and anti-inflammatory effect.[33,105,106] Studies assessing the effect of antiplatelet drugs on hypercoagulability and outcome in COVID-19 patients are actually under clinical investigation (NCT04365309, NCT04368377).

In summary, COVID-19-associated coagulopathy is characterized by hypercoagulability and associated with a high incidence of VTE and PE and poor outcome in patients with COVID-19. Here, biomarkers of coagulation (such as D-dimer, fibrinogen, platelet count), inflammation (such as IL-6) and immunity (such as lymphocyte count) as well as clinical scoring systems (such as SOFA, ISTH DIC and SIC score) can be helpful in predicting clinical course, need for hospital resources (such as ICU beds, intubation and ventilator therapy, and ECMO) and patient's outcome in patients with COVID-19. However, COVID-19 associated coagulopathy

is still incompletely understood and therapeutic options are limited to unspecific supportive therapy. Whether viscoelastic and platelet function testing can provide additional value in predicting clinical course, need for hospital resources and patient's outcome or in guiding anticoagulation in COVID-19 patients is actually under investigation (ROHOCO study).

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Figure Legends

Figure 1. Pathophysiology of sepsis-induced coagulopathy (SIC)/COVID-19-associated coagulopathy and effects on viscoelastic testing variables (as shown in the in blue boxes). DAMPs, damage-associated molecular patterns; DIC, disseminated intravascular coagulation; IL-6, interleukin 6; MOF, multiple organ failure; NF-kappaB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAI-1, plasminogen activator inhibitor type 1; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; TF, tissue factor.

Figure 2. Thromboelastometry triad of thrombosis. VET, viscoelastic testing.

Figure 1

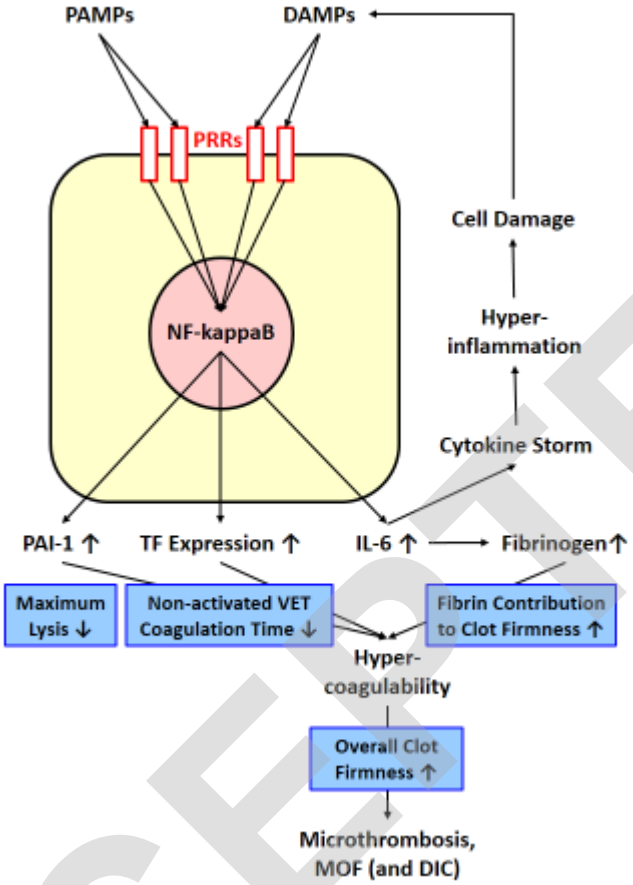

Figure 2