Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Research 200 (2021) 1–8

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Mechanisms of thrombosis and cardiovascular complications in COVID-19

Eden M. Page, Robert A.S. Ariëns *

Discovery and Translational Science Department, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Thromboembolism
Cardiovascular complications
D-dimer

ABSTRACT

Background: The novel coronavirus SARS-CoV-2, responsible for the 2019–2020 global (COVID-19) pandemic, is a respiratory virus associated with the development of thromboembolic complications and respiratory failure in severe cases. Increased risk of pulmonary embolism and thrombosis has been identified in COVID-19 patients, alongside accompanying elevations in potential prognostic biomarkers, including D-dimer, IL-6 and cardiac specific troponins. Our aim was to provide a scoping review of the available literature regarding thrombosis risk, other cardiovascular implications, and their biomarkers in COVID-19 to highlight potential disease mechanisms.
Methods: Authors conducted a literature search in PubMed using MeSH headings "disseminated intravascular coagulation", "pulmonary embolism", "thromb*", "stroke", "myocardial infarction" and "acute lung injury", as well as terms "COVID-19", "SARS-CoV-2", "2019 novel coronavirus" and "2019-nCoV".
Results and conclusions: COVID-19 disease is characterised by the interactions between hyperactive coagulation and complement systems – induced by hyper-inflammatory conditions, resulting in a pro-thrombotic state and diffuse tissue injury. There are several promising prognostic markers of disease severity, with D-dimer the most significant. The presence of thrombocytopenia appears to be a key indicator of patient deterioration.
Further research is required to understand the underlying pathophysiology in COVID-19 and its implications in disease progression and patient management. Randomised trials are urgently needed to determine the safety of proposed therapeutic anticoagulation with heparin and the role for anti-platelet agents, such as Ticagrelor, in patient management.

1. Introduction

The novel coronavirus known as SARS-CoV-2, is a respiratory virus that presents with symptoms such as a non-productive cough (60–80%), fever (90%) and shortness of breath (19–40%) [1] and is responsible for the 2019–2020 global coronavirus disease (COVID-19) pandemic. Although most patients experience mild or no symptoms, severe disease is associated with thromboembolic complications and respiratory failure. There is an observed rise in the clinical manifestations of the disease 7 to 14 days after initial symptom onset [2]. Related coronaviruses SARS-CoV-1 and MERS-CoV, which were responsible for outbreaks in 2003 and 2012 respectively, are also associated with thrombotic complications, with a 30% VTE incidence reported in critical SARS-CoV-1 cases [3]. Understanding the thrombotic manifestations of the virus is important for patient management and the underlying pathophysiology of SARS-CoV-2 infection.

2. Method

We conducted a literature search in PubMed using the cardiovascular MeSH headings "disseminated intravascular coagulation", "pulmonary embolism", "thromb*", "stroke", "myocardial infarction" and "acute lung injury" as well as the terms "COVID-19", "SARS-CoV-2", "2019 novel coronavirus" and "2019-nCoV". Only studies published in English after January 1st 2019 were included. This search identified 195 papers. Due to the rapid publication rate of COVID-19 research, many of the articles were published pre-print. Following review, a total of 45 articles were selected. The main criteria for exclusion of papers were: 1) single case reports, and 2) reports on the management of non-COVID-19 illness in the context of the pandemic. Further relevant papers were included after supplementary reading, the majority of which relate to the underlying mechanisms of the complement cascade and inflammatory response.

* Corresponding author.
E-mail address: R.A.S.Ariens@leeds.ac.uk (R.A.S. Ariëns).

https://doi.org/10.1016/j.thromres.2021.01.005
Received 30 September 2020; Received in revised form 16 December 2020; Accepted 8 January 2021
Available online 18 January 2021

3. Thrombotic complications and mechanisms

There is substantial and mounting evidence for a significant risk of thrombosis in patients with COVID-19. A study in Dutch hospitals by Klok et al. found a 31% incidence of thromboembolic events in 184 COVID-19 ICU patients, despite low molecular weight heparin (LMWH) thromboprophylaxis [4]. Complications included pulmonary embolism (PE), deep-vein thrombosis (DVT), ischaemic stroke, myocardial infarction and systemic arterial embolism. Acute PE made up as much as 81% of all complications observed (n = 25) [4]. In COVID-19, venous thromboembolic (VTE) complications are more prevalent in ICU patients at 59% incidence (95% CI 42–72) compared to 9.2% on the ward (95% CI 2.6–21) and associated with increased mortality (Adjusted HR = 2.4, 95% CI = 1.02–5.5) [5]. Patients in ICU with SARS-CoV-2 are also more likely to develop VTE than non-COVID-19 ICU patients [6], which suggests that the underlying cause of VTE in COVID-19 is likely more than the immobility due to ICU treatment alone. SARS-CoV-2 patients with VTE are older and likely to demonstrate abnormal coagulation parameters, such as D-dimer and APTT [7].

The main risk factors for venous thrombosis classically involve stasis, endothelial injury and a hypercoagulable state, together known as Virchow's triad. A number of lifestyle and clinical factors, including immobility, obesity, dehydration, pregnancy, surgery and active cancer can contribute to Virchow's triad-mediated venous thrombosis. Inflammation contributes to thrombosis through endothelial injury and perpetuating a hypercoagulable state via a reduction in fibrinolysis, stimulation of the tissue factor pathway and NETosis. The release of neutrophil extracellular traps (NETs) from neutrophils occurs through a specialised mechanism (NETosis) involving the release of condensed chromatin and neutrophil granule contents, in response to inflammation. Complement activation is also thought to be heavily involved in thrombosis: C3a and membrane attack complex (C5b-9) are both involved in platelet activation and C5a increases plasma and cellular TF expression [8]. The interplay between inflammation, complement activation and the coagulation cascade is thought to be crucial to understanding the pathophysiology of COVID-19 and is responsible for triggering disseminated intravascular coagulation (DIC).

In COVID-19, pulmonary micro-thrombosis in the lung alveoli distinct from pulmonary embolism has also been reported, with a study by Dohlnikoff et al. identifying fibrinous thrombi in the pulmonary arterioles in 8 out of 10 cases analysed with ultrasound-based autopsy techniques [9]. These intravascular pulmonary microthrombi have been linked to the development of hypoxemia in the early stages of adult respiratory distress syndrome (ARDS) in COVID-19 [10], which is likely due to a ventilation/perfusion mismatch created by changes in microcirculatory blood flow and a subsequent increase in dead space. Primary pulmonary thrombosis could be underpinned by the proposed mechanisms of pulmonary angiotensin converting enzyme 2 (ACE2) mediated endothelial injury, potential cytokine storm and the development of a hypercoagulable state in COVID-19 (Fig. 1.) [11,12].

It appears that pulmonary thrombosis (PT) is not always preceded by DVT in COVID-19, and originates primarily from the lungs instead of embolising from the venous circulation [11–13]. In a recent study, DVT incidence in COVID-19 patients was just 1.6%, whilst PE was the most common pathological outcome [4]. However, it is important to note that no active DVT screening was done in unsuspected patients [4,14], and a different study, which performed autopsies on 12 consecutive COVID-19 patients, found evidence of DVT in 7, despite it not being previously suspected [15]. Cattaneo et al. also support the concept of primary PT and comment on filling defects identified in pulmonary arterioles as partially occlusive, which is more frequently seen in PT than PE [13]. If PT is occurring in SARS-CoV-2 infection rather than PE, then diagnostic

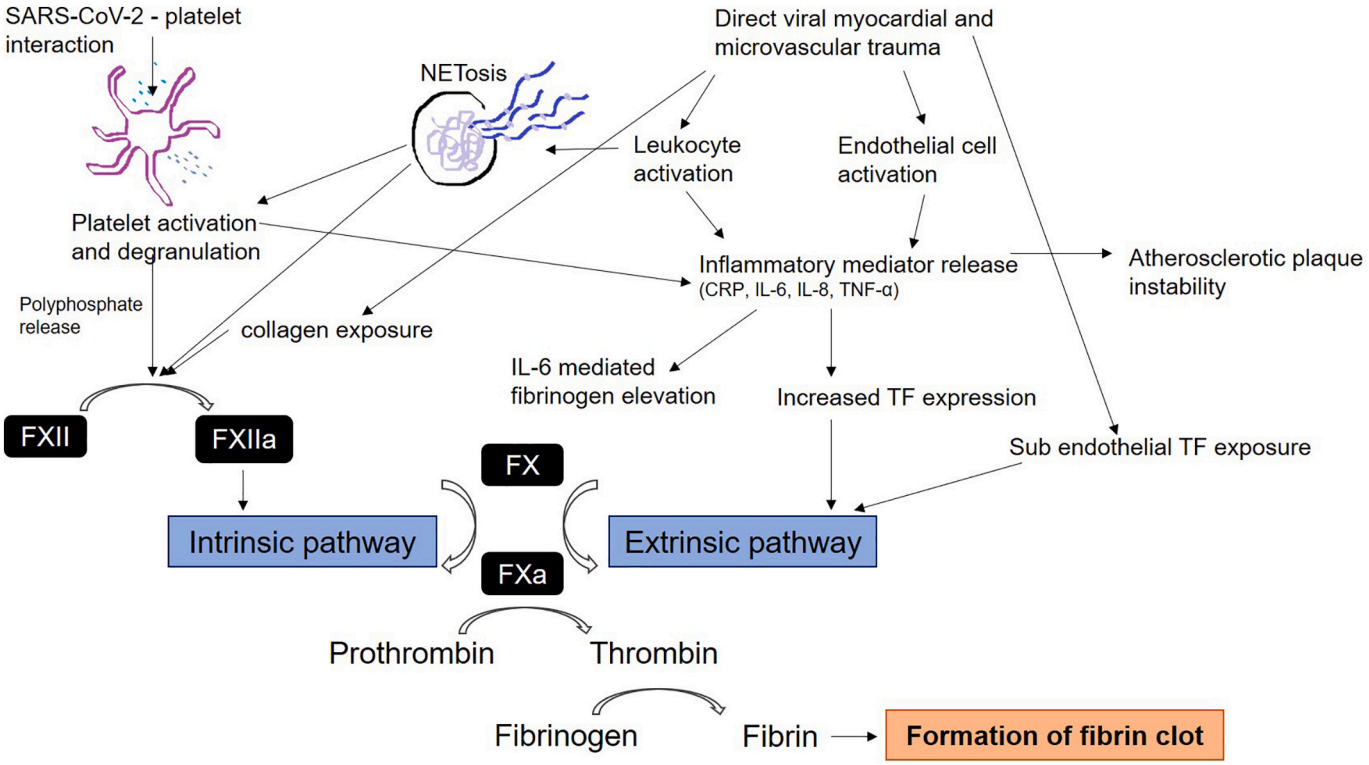

Fig. 1. Proposed mechanisms of immunothrombosis in COVID-19 and the interactions of the inflammation and coagulation systems. Direct SARS-CoV-2 – platelet interaction results in high levels of platelet activation, promoting a pro-thrombotic state. Direct viral trauma and resultant inflammation leads to fibrinogen elevations through IL-6, leukocyte activation, NETosis, endothelial cell activation and inflammatory mediator release. Subsequent activation of both the tissue factor and contact activation pathways of the coagulation cascade further potentiates a hyper-coagulable state, which leads to the development of thromboembolic complications in patients. CRP = C-Reactive Protein, IL-6 = Interleukin 6, IL-8 = Interleukin 8, TNF-α = Tumour necrosis factor α, TF = Tissue factor, FXII = coagulation factor XII, FXIIa = activated coagulation factor XII, FX = coagulation factor X, FXa = activated coagulation factor X.

methods using DVT predictors such as the Wells pretest probability score may need to be adapted or replaced [11]. Van Nieuwkoop et al. also questioned whether the difference in pathophysiology between PE and PT would have implications for anticoagulant treatment [12].

SARS-CoV-2 is able to potentiate a hyper-coagulable state via activation of the contact and tissue factor pathways [16,17]. Direct viral myocardial and microvascular injury causes subendothelium and collagen exposure, contributing to platelet activation and possible contact pathway activation which could be hypothesised to follow polyphosphate release in platelet degranulation. Endothelial trauma causes tissue factor (TF) exposure in the sub-endothelium, activating the tissue factor pathway via the cleavage of FVII to FVIIa. ACE-2-SARS-CoV-2 interactions may also dysregulate the kallikrein/kinin system, further contributing to contact pathway activation [12].

Inflammation due to SARS-CoV-2 involves primary vessel inflammation, possible sepsis and a secondary reaction to tissue damage caused by the virus [7], and includes the generation of inflammatory mediators such as C-Reactive protein (CRP), Interleukin 6 (IL-6), Interleukin-8 (IL-8) and tumour necrosis factor α (TNF-α) [2,18]. Inflammatory mediator release results in increased TF expression [19], whilst IL-6 is a key regulator of fibrinogen transcription [20]. Increased IL-6 levels are associated with increased plasma fibrinogen levels [20], which is congruent with the drastic rise in plasma fibrinogen observed in COVID-19 patients [17].

'Cytokine storm' is a term used to describe the acute overproduction of pro-inflammatory cytokines by innate immune cells observed in certain inflammatory infections. A cytokine storm is typically associated with concurrent serum ferritin rises and haemodynamic instability, leading to vascular damage, multi-organ failure and acute lung injury [21], all of which have been previously identified in COVID-19 [18,21,22]. The existence of a cytokine storm picture in COVID-19 has been contested, with those arguing that it should be described as a hypo-inflammatory vasculopathy instead [23], however accumulating evidence indicates convincing clinical parallels between severe COVID-19, markedly raised cytokines (IL-6, IL-10, IL-2R, IL-8, TNF-α) and broader signs of organ failure and cell damage [18,21]. There is also evidence of platelet cytokine release contributing to plasma cytokine levels [24].

SARS-CoV-2 – platelet interactions result in platelet activation and degranulation in COVID-19, further potentiating the pro-thrombotic vascular milieu [25]. Polyphosphate release from activated platelet dense granules drives intrinsic pathway activation via the activation of FXII [26]. Coagulation activity results in the conversion of fibrinogen to fibrin via thrombin generation and subsequent fibrin polymerisation. Furthermore, platelet uptake of SARS-CoV-2 is highly suspected, yet there is no evidence of ACE2 expression on activated platelets in COVID-19 patients [25]. Despite this, mRNA from the SARS-CoV-2 N1 gene has been detected in patient platelet samples [25], indicating a possible alternative mechanism of viral uptake. Other viruses, such as influenza, are known to be endocytosed by platelets, resulting in TLR7 mediated C3 release and NETosis [27]. SARS-CoV-2 RNA is thought to interact with platelets via TLR7 and TLR9 in a similar way to activate leukocytes and stimulate inflammatory cytokine release [16]. Another recent study indicated sialoglycan binding as a possible explanation for influenza virus platelet uptake and subsequent thrombocytopenia in virulent strains [28]. Interestingly, there is also recent evidence of sialoglycan-spike glycoprotein interaction mediated entry for other coronaviruses, such as SARS-CoV-1 [29,30], as well as SARS-CoV-2. [30] Future studies targeting this mechanism of cell entry may be needed to investigate its role in COVID-19 disease.

Evidence suggests that NETosis is increased in COVID-19, especially in severe disease [31]. NETs effectively trap viruses, fungi and bacteria, whilst concentrating anti-microbial factors [32] Despite being an important part of the immune response, NET formation also interacts with the inflammatory and coagulation cascades, contributing to acute lung injury and platelet, endothelial cell and FXII activation [32,33]. NETs further increase the resistance of clots to fibrinolysis [34,35]. Further research is needed to determine the role of NET formation in COVID-19, especially due to the strong links between NET formation and respiratory conditions such as Acute Respiratory Distress Syndrome (ARDS) [32]. NETosis is one of the key mechanisms that connects inflammatory mediator release, platelet and endothelium activation, clot formation and resistance to fibrinolysis (Fig. 1).

The balance between thrombus deposition and thrombolysis is delicately maintained by tissue-type plasminogen activator (tPA), urinary-type plasminogen activator (uPA) and their inhibitor plasminogen activator inhibitor-1 (PAI-1). Impaired tPA and uPA fibrinolytic function could further perpetuate a pro-thrombotic state in COVID-19 patients, whilst an increase in spontaneous fibrinolytic activity, could cause a rare, but significant, bleeding profile [36]. Evidence for both thrombosis and bleeding has been found in COVID-19 [36], and the presence of fibrinolytic hyperactivity is supported by significant rises in D-dimer [37]. Pro-inflammatory cytokine release may trigger endothelial cell activation and the release of PAI-1 and tPA [36]. It has been hypothesised that PAI-1 dominates tPA in COVID-19 to reduce thrombolysis, supported by thromboelastography data indicating a reduction in COVID-19 patient clot lysis [36,37].

Disseminated intravascular coagulation is a potentially lethal mechanism in COVID-19 that leads to fibrinolysis derangement and multi-organ dysfunction [38]. Clinical signs of an overt DIC include thrombocytopenia, prolonged PT, elevated D-dimer and increased fibrin degradation products [38]. Sepsis-induced coagulopathy (SIC) is a term used to identify early DIC, where platelet count and prothrombin time are still significantly deranged in a patient with confirmed sepsis [38]. The pathophysiology behind DIC in sepsis is widely accepted as involving a combination of different mechanisms, including endothelial cell activation, platelet activation, leukocyte activation and fibrin deposition, resulting in diffuse inflammation and coagulopathy. Overall DIC incidence has previously been reported as 2.2% in hospitalised COVID-19 patients [39]. However, there is an emerging disparity between surviving and non-surviving cohorts, with 71.4% of non-survivors meeting International Society of Thrombosis and Haemostasis (ISTH) DIC criteria compared with just 0.6% of the survivors [40]: suggesting that DIC may be a critical sign of patient deterioration.

One discussion point with systemic DIC as an underlying process in COVID-19 is the apparent lack of bleeding in patients [41,42]. Based on this, Marongiu et al. proposed localised pulmonary intravascular coagulation as an alternative process in COVID-19 [42]; However, there has been some debate about the contradictory concept of a localised DIC [43]. Others have also proposed a pulmonary intravascular coagulation mechanism, stemming from the type II pneumocyte/endothelial cell ACE2 receptor interaction with SARS-CoV-2 [44].

It has also been suggested that the phenotype of COVID-19 microthrombus formation aligns more closely with complement-mediated thrombotic microangiopathy than either sepsis-induced coagulopathy or DIC [45]. This is supported by the additional presence of anaemia, LDH elevation and renal dysfunction in severe cases [15,45]. SARS-CoV-2 is hypothesised to cause microvascular dysfunction via ACE2 receptor interactions and to activate Mannan-binding lectin serine protease 2 (MASP-2) in the lectin pathway of complement activation, which are two different candidate mechanisms behind complement involvement in COVID-19 disease [45]. In vitro studies have suggested that MASP-1 and MASP-2 can cleave prothrombin to form thrombin and activate both fibrinogen and FXIII [8] [46–48]. Future studies are needed to specifically address the role of MASPs in COVID-19 related disease mechanisms.

4. Other cardiovascular complications

Another key cardiovascular complication reported in COVID-19 is acute cardiac injury, which has been observed in 7–28% of hospitalised patients and is associated with an increased risk of severe disease and death [1]. Interestingly, there is an apparent delay between initial

symptom onset and the development of myocardial damage [49]. Acute cardiac injury may be due to virus-mediated lysis of cardiomyocytes, which is also observed in other viral infections, or as a consequence of SARS-CoV-2 binding ACE2 receptors in the heart [50,51]. ACE2 receptors are widely expressed in tissues such as lung epithelium, myocardium, kidneys and vascular endothelium [1]. ACE2 cleaves angiotensin II into the vasodilator angiotensin I, opposing the action of ACE1 that produces the vasoconstrictor angiotensin II in the Renin-Angiotensin-Aldosterone system (RAAS) [1]. SARS-CoV-2 binding to ACE2 receptors reduces the activity of ACE2 and may dampen the cardioprotective effects of the enzyme [50,52].

Myocarditis has been suspected in multiple COVID-19 cases, but the true incidence is unknown as the required histology tests are often incomplete [53]. However, recent work by Wenzel et al. has identified SARS-CoV-2 in endomyocardial biopsies of 2 patients with previous COVID-19 infection and suspected myocarditis [54]. The interplay between inflammation and myocardial injury is thought to be responsible for the suspected myocarditis in COVID-19 [55], and both could individually contribute to the observed pro-coagulative state via immunothrombosis (Fig. 1). Inflammation resulting in substantial cytokine release can also result in atherosclerotic plaque instability and subsequent arterial thrombus formation [50,51,56]. Cytokines increase inflammatory cell migration and plaque infiltration, contributing to atherosclerosis and plaque instability [56]. Atherosclerotic plaque rupture can lead to coronary thrombosis and acute myocardial infarction [51]. COVID-19 Patients with underlying risk factors for atherosclerosis, such as hypertension and diabetes are much more likely to develop disease requiring ICU admission (2-fold and 3-fold increased risk respectively) and more likely to reach fatal endpoint (6% and 7.3% vs 2.3%) [51].

5. Cardiovascular/inflammatory biomarkers in COVID-19

Several haemostatic and inflammatory biomarkers have been explored in COVID-19 patients for possible monitoring of patients and their treatment, including D-Dimer, established clotting tests (Prothrombin time (PT) and Activated Partial Prothrombin Time (APTT)), full blood counts and inflammatory markers (Fig. 2). Currently, guidance from the ISTH recommends the use of D-dimer levels, PT and platelet count in all COVID-19 patients, with D-dimer considered the most important [57]. PAI-1 and tPA levels have been observed to mirror rises in other, potentially stronger, prognostic biomarkers such as D-dimer and platelet count, demonstrating the significance of the fibrinolytic system in the mechanisms underlying COVID-19 [36]. It has been suggested that tPA and PAI-1 elevation could be associated with increased mortality and poorer lung function in patients [36]. However, many of the studies investigating prognostic biomarkers in COVID-19 have thus far not included tPA or PAI-1 measurements.

Further work is required to determine the role of predictive markers in mild and moderate disease as the majority of current research is conducted in severe patients admitted to hospital, and often intensive care.

5.1. D-dimer

D-dimer is a marker of cross-linked fibrin formation and breakdown with a high (negative) predictive value for PE. In patients without underlying VTE, a normal D-dimer level of <0.5 μg/mL would be expected. In a study by Helms et al. of 150 COVID-19 ICU patients with ARDS, using the same reference range, >95% had elevated D-dimer levels [41]. D-dimer has been proposed as an important prognostic marker for mortality in COVID-19 disease [6,58,59]. Patients with raised D-dimer levels are much more likely to have significant underlying disease, such as diabetes and hypertension [59], which predisposes to worse outcome. D-dimer elevation supports the mechanism of increased fibrin network turnover as a result of tissue injury and inflammation. It has also been suggested that D-dimer levels could be a useful tool for monitoring anticoagulant response, as D-dimer levels decrease following successful treatment [7]. An association between D-dimer values >1 μg/mL and increased in-hospital mortality (Adjusted HR = 18.4, 95% CI = 2.6–128.6) was reported in a study of 199 patients [58]. Another report found a similar link but with D-dimer levels >2 μg/mL in a study of 343 patients [59]. It has been suggested that 2 μg/mL, which is a fourfold increase from the 0.5 μg/mL reference range upper limit, could be used as a D-dimer cut off level for pre-empting mortality (sensitivity 92.3%, specificity 83.3%) [59], however further studies are needed to confirm

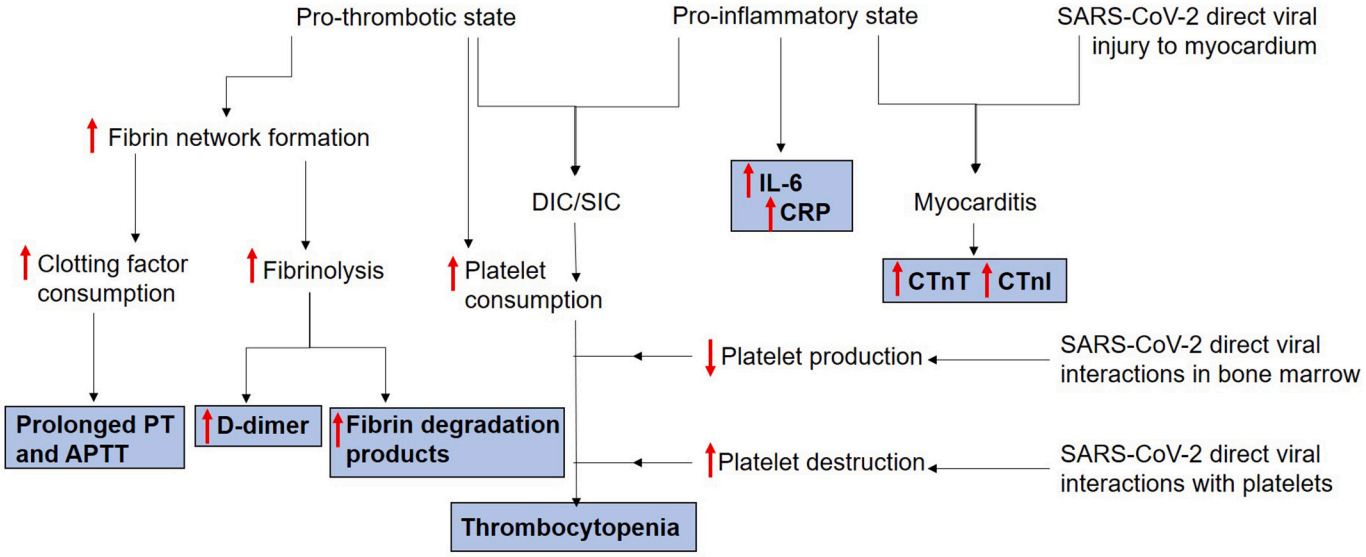

Fig. 2. Proposed mechanisms behind the changes in prognostic biomarkers observed in COVID-19. Increased fibrin network turnover results in clotting factor consumption and prolonged standard clotting tests (PT and APTT), as well as raised D-dimer and fibrin degradation products as a result of plasmin activity. Inflammatory markers CRP and IL-6, as well as myocardial damage markers CTnT and CTnI, are elevated in COVID-19. Thrombocytopenia results from a combination of increased activation, reduced production and increased destruction due to the direct effects of SARS-CoV-2 viral interactions and the development of DIC/SIC in severe disease. PT = Prothrombin Time, APTT = Activated Partial Thromboplastin Time, IL-6 = Interleukin 6, CRP = C-Reactive Protein, CTnT = Cardiac Specific Troponin T, CTnI = Cardiac Specific Troponin I, DIC = Disseminated Intravascular Coagulation, SIC = Sepsis-Induced Coagulopathy.

this and establish reliable cut-off values. An important current limitation is the use of different D-dimer assay kits with different sensitivity and specificity in different studies, which explains the variability of the findings. International standardisation studies are required to address this limitation.

5.2. Thrombocytopenia

Thrombocytopenia (platelet count <140 × 10^9/L) is the result of changes in the rate of platelet consumption, destruction or production. Virus associated thrombocytopenia is common, and multiple viruses interfere with haematopoiesis in the bone marrow, including SARS-CoV-1 [60]. An increase in platelet consumption is also expected in COVID-19 due to intravascular pulmonary microthrombus formation [10], endothelial damage and platelet hyper-reactivity, characterised by an increase in platelet-monocyte, platelet-neutrophil and platelet-T-cell interactions [25]. A retrospective study in Wuhan, China, identified a reduced platelet count in 20.7% of consecutive COVID-19 patients (n = 1476) admitted during the pandemic [60]. However, COVID-19 associated thrombocytopenia rarely results in a bleeding phenotype, with only 2.7% of patients experiencing haemorrhagic complications [41]. Platelet counts <50 × 10^9/L are rarely seen in COVID-19 disease [10]. Thrombocytopenia is also part of the classical DIC presentation seen in COVID-19 along with elevated fibrin degradation products, D-dimer and prolonged clotting tests.

Platelet counts show promise as a prognostic marker in COVID-19, with thrombocytopenia being associated with over a five-fold increased risk of severe disease [61]. There is also a disparity between survivors and non-survivors, with very low platelet counts being associated with increased mortality [10,60,61]. One retrospective study (n = 1476) reported in-hospital mortality rates of 92.1%, 61.2%, 17.5% and 4.7% in patients with platelet counts of <50, 50–100, 100–150 and >150 × 10^9/L respectively [60]. Based on these findings, monitoring platelet count in COVID-19 disease may play an important role in patient management.

5.3. Inflammatory markers

COVID-19 triggers a pro-inflammatory state in many patients as a result of direct viral tissue injury and the immune responses against the virus. These changes are thought to occur in the majority of patients, including those classed as mild or moderate [62]. Observed changes include a rise in inflammatory markers such as C-reactive protein (CRP), fibrinogen, ferritin, Interleukins 2, 6 and 7 (IL-2, IL-6 and IL-7) and Tumour necrosis factor α (TNF-α) [2,49,62,63]. Inflammatory marker elevation coincides with the surge in clinical symptoms that is observed 7 to 14 days after initial onset [2].

A retrospective cohort study in Wuhan, China, found that non-surviving patients had higher IL-6 levels than survivors (11.0 pg/mL vs 6.3 pg/mL, $p < 0.0001$) throughout the duration of illness. IL-6 levels also rose further as patient condition deteriorated [58]. IL-6 levels are considered useful in distinguishing different severities/profiles of COVID-19 disease [64]. The findings of this retrospective study [58] contradict another smaller retrospective study [63], which showed that IL-6 levels decreased during ICU admission. Interestingly, one study speculated that IL-6 elevation is a possible protective factor in COVID-19 and may be used as a possible explanation for the apparent decrease in ischaemic stroke presentations to A&E departments in Italy [62].

CRP is also elevated in the majority (60.7%) of hospitalised COVID-19 patients [65]. CRP is more likely to be elevated in severe disease than in mild or moderate disease (81.5% vs 56.4%, $p < 0.001$) and patients with elevated levels were more likely to experience composite endpoints (ICU admission, mechanical ventilation or death) (91.1% vs 58.8%, $p < 0.001$) [2,65]. Furthermore, CRP levels have been linked with elevated cardiac troponins (see below) and myocardial injury [2].

Finally, serum ferritin could also be considered as a potential prognostic inflammatory marker in COVID-19, as well as a marker of cellular damage. Serum ferritin elevation on admission has been shown to be significantly associated with ICU admission and in-hospital mortality, following adjustment for demographics ($p = 0.007$, n = 131) [22].

5.4. Clotting tests

Coagulopathy can be identified with clotting tests that measure the basic functions of the clotting cascade, such as the PT and APTT. Multiple studies have reported prolonged PT (>3 s) and APTT (>5 s) in patients in ICU with COVID-19 [4,66,67], supporting the presence of a hyper-coagulable state. There is more debate over the usefulness of PT and APTT as prognostic markers than for D-dimer levels, as the PT and APTT are less specific, and the degree of change in these tests due to hypercoagulability is relatively small. A study by Cui et al. [7] found that PT and APTT were not significantly higher in COVID-19 VTE patients compared to non-VTE patients, whilst Roncon et al. [67] suggested that PT and APTT can be used to predict thrombotic complications. The debate seems to be centred more on their use as prognostic markers rather than their ability to identify the presence of coagulopathy in COVID-19.

Interestingly, the PT has been shown to increase from ICU admission baseline to day 10, whilst APTT was higher on admission and slowly decreased across the same period [63]. A clear advantage of the PT and APTT is their relatively high degree of standardisation and wider availability in general hospital laboratory settings, unlike some of the other biomarkers (e.g. D-dimer and IL-6).

5.5. Cardiac specific troponins

Troponins T (cTnT) and I (cTnI) are highly sensitive cardiac-specific markers of myocardial damage that are released into the blood following heart trauma or infection. Troponin elevation is traditionally associated with myocardial infarction, myocarditis and acute PE resulting in myocardial ischaemia. Initial retrospective papers suggested troponin is consistently elevated in patients with COVID-19 and could be considered a marker of poor prognosis, with elevation more frequent observed in ICU patients and non-survivors [50,53,58,68]. However, a recent prospective study suggests that troponin levels on admission are not significantly correlated with ICU admission or in-hospital mortality after adjustment for sex, age, ethnicity, co-morbidities and symptom duration [22].

6. Implications for anti-coagulation

Due to the increased risk of venous thromboembolism in patients with COVID-19 disease, it is currently recommended that all hospitalised patients are given routine heparin thromboprophylaxis if there are no additional bleeding risks [57,64]. It has also been proposed that prophylactic dose may need to be increased as the risk of VTE remains high in patients on standard prophylactic doses [4,69]. One study that actively screened for VTE in 26 consecutive COVID-19 ICU patients found that VTE incidence was significantly higher in patients on prophylactic anticoagulation compared to those on therapeutic anticoagulation (100% vs 56%, $p = 0.03$) [70]. Furthermore, therapeutic heparin doses may have the additional benefit of counteracting the resistance to treatment that occurs in patients with drastically raised fibrinogen levels [71]. Further randomised control trials are urgently needed to rectify the absence of reliable, large scale datasets and to understand the consequences of therapeutic vs prophylactic heparin dosage to guide prescription and modify guidelines.

Although the ISTH guidance recommends LMWH prophylaxis [57], a report by Barrett et al. [71] recommends the use of therapeutic unfractionated heparin in patients. Reasons for this include an increased risk of renal failure following ARDS (for which UFH is preferred) and the existence of the UFH protamine sulphate antidote [71]. In response,

Thachil et al. [72], referred to the practical merits of LMWH vs UFH and that fibrinogen elevation in COVID-19 would affect UFH more. Guidelines by Zhai et al. recommend low molecular weight heparin (LMWH) as first-line therapy and unfractionated heparin (UH) in patients with creatinine clearance <30 mL/min [73]. Both UFH and LWMH may provide additional benefits in COVID-19 due to their secondary anti-inflammatory effects [74].

As previously stated, ISTH guidance recommends that all hospitalised COVID-19 patients should be given thromboprophylaxis, even if non-critical [57]; However, a recent study found that heparin therapy only improved mortality in patients who met SIC criteria (40.0% vs 64.2%, $p = 0.029$) or had a markedly increased (>3.0 μg/mL) D-dimer (32.8% vs 52.4%, $p = 0.017$) [75]. It should be stressed that further research is required [12]. This would avoid unnecessary anti-coagulation and its associated side-effects, such as heparin-induced thrombocytopenia [76].

Ticagrelor, which inhibits platelet ADP receptor P2Y12 to block platelet activation and aggregation, has been proposed as alternative thromboprophylaxis [77]. Ticagrelor has been shown to reduce lung injury acquired in pneumonia [77] and prevent SIC/DIC development by reducing inflammatory mediator levels (IL-6, TNF-α, IL-8) and limiting NETosis [76]. Acute lung injury, inflammation and SIC are all key parts of COVID-19 pathophysiology. Randomised control trials are required to determine the efficacy of Ticagrelor in COVID-19. Ticagrelor therapy is currently only available for oral administration, making it unsuitable for mechanically ventilated patients. A similar P2Y12 inhibitor, Cangrelor, has recently been licensed as an IV alternative, however, there are no research papers or clinical trials documenting its efficacy in COVID-19 cohorts.

All anti-coagulants have associated risks of bleeding, which should be weighed against the clinical anti-thrombotic benefit. This risk should be considered on a patient-by-patient basis, taking into account potential coagulopathies and renal insufficiency.

7. Concluding remarks

The interplay between the inflammatory, coagulation and complement systems in COVID-19 requires further research, to establish their mechanistic contributions to the pathophysiology of the disease in further detail. Understanding the balance of these systems is vital for the establishment of optimal management and treatment strategies, particularly in the case of pulmonary micro-thrombosis vs pulmonary embolism and DIC/SIC vs complement-mediated microthrombus formation. Randomised control trials are urgently needed to determine the safety of proposed therapeutic heparin anticoagulation and the role for anti-platelets, such as Ticagrelor, in patient management.

With further data in these key areas of research and trials, we should be able to substantially improve the treatment and prevention of COVID-19 related thrombosis and other cardiovascular complications in the near future. With the number of positive cases increasing worldwide, and in view of the development of secondary and further future outbreaks in many places across the globe, this research endeavour is going to become increasingly important.

Funding

EMP is supported by an EXSEL Scholarship (https://medicinehealth.leeds.ac.uk/medicine-undergraduate-mbchb/doc/student-excellence-scheme-1). RASA is supported by a British Heart Foundation Programme Grant (RG/18/11/34036) and a Wellcome Trust Investigator Award (204951/B/16/Z).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] D. Atri, H.K. Siddiqi, J. Lang, V. Nauffal, D.A. Morrow, E.A. Bohula, COVID-19 for the cardiologist: a current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential therapeutic strategies, JACC Basic Transl Sci. 5 (2020) 518–536, https://doi.org/10.1016/j.jacbts.2020.04.002.
[2] E. Terpos, I. Ntanasis-Stathopoulos, I. Elalamy, E. Kastritis, T.N. Sergentanis, M. Politou, T. Psaltopoulou, G. Gerotziafas, M.A. Dimopoulos, Hematological findings and complications of COVID-19, Am. J. Hematol. 95 (2020) 834–847, https://doi.org/10.1002/ajh.25829.
[3] D. Giannis, I.A. Ziogas, P. Gianni, Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past, J. Clin. Virol. 127 (2020) 104362, https://doi.org/10.1016/j.jcv.2020.104362.
[4] F.A. Klok, M.J.H.A. Kruip, N.J.M. van der Meer, M.S. Arbous, D.A.M.P.J. Gommers, K.M. Kant, F.H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (2020) 145–147, https://doi.org/10.1016/j.thromres.2020.04.013.
[5] S. Middeldorp, M. Coppens, T.F. van Haaps, M. Foppen, A.P. Vlaar, M.C.A. Müller, C.C.S. Bouman, L.F.M. Beenen, R.S. Kootte, J. Heijmans, L.P. Smits, P.I. Bonta, N. van Es, Incidence of venous thromboembolism in hospitalized patients with COVID-19, J. Thromb. Haemost. 18 (2020) 1995–2002, https://doi.org/10.1111/jth.14888.
[6] A. Kollias, K.G. Kyriakoulis, E. Dimakakos, G. Poulakou, G.S. Stergiou, K. Syrigos, Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action, Br. J. Haematol. 189 (2020) 846–847, https://doi.org/10.1111/bjh.16727.
[7] S. Cui, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, J. Thromb. Haemost. 18 (2020) 1421–1424, https://doi.org/10.1111/jth.14830.
[8] A. Fletcher-Sandersjöö, B.M. Bellander, Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review, Thromb. Res. 194 (2020) 36–41, https://doi.org/10.1016/j.thromres.2020.06.027.
[9] M. Dolhnikoff, A.N. Duarte-Neto, R.A. de Almeida Monteiro, L.F.F. da Silva, E.P. de Oliveira, P.H.N. Saldiva, T. Mauad, E.M. Negri, Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19, J. Thromb. Haemost. 18 (2020) 1517–1519, https://doi.org/10.1111/jth.14844.
[10] J. Thachil, What do monitoring platelet counts in COVID-19 teach us? J. Thromb. Haemost. 18 (2020) 2071–2072, https://doi.org/10.1111/jth.14879.
[11] M. Gabrielli, P. Lamendola, A. Esperide, F. Valletta, F. Franceschi, COVID-19 and thrombotic complications: pulmonary thrombosis rather than embolism? Thromb. Res. 193 (2020) 98, https://doi.org/10.1016/j.thromres.2020.06.014.
[12] C. van Nieuwkoop, COVID-19 associated pulmonary thrombosis, Thromb. Res. 191 (2020) 151, https://doi.org/10.1016/j.thromres.2020.04.042.
[13] M. Cattaneo, E.M. Bertinato, S. Birocchi, C. Brizio, D. Malavolta, M. Manzoni, G. Muscarella, M. Orlandi, Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? Thromb. Haemost. 120 (2020) 1230–1232, https://doi.org/10.1055/s-0040-1712097.
[14] R.J. Rosen, Thrombotic complications in critically ill patients with COVID 19, Thromb. Res. 191 (2020) 56, https://doi.org/10.1016/j.thromres.2020.04.032.
[15] D. Wichmann, J.P. Sperhake, M. Lütgehetmann, S. Steurer, C. Edler, A. Heinemann, F. Heinrich, H. Muschumba, I. Kniep, A.S. Schröder, C. Burdelski, G. de Heer, A. Nierhaus, D. Frings, S. Pfefferle, H. Becker, H. Bredereke-Wiedling, A. de Weerth, H.R. Paschen, S. Sheikhzadeh-Eggers, A. Stang, S. Schmiedel, C. Bokemeyer, M.M. Addo, M. Aepfelbacher, K. Püschel, S. Kluge, Autopsy findings and venous thromboembolism in patients with COVID-19, Ann. Intern. Med. (2020) M20–2003, https://doi.org/10.7326/M20-2003.
[16] M. Bautista-Vargas, F. Bonilla-Abadía, C.A. Cañas, Potential role for tissue factor in the pathogenesis of hypercoagulability associated with in COVID-19, J. Thromb. Thrombolysis (2020), https://doi.org/10.1007/s11239-020-02172-x [published online ahead of print].
[17] J.M. Connors, J.H. Levy, COVID-19 and its implications for thrombosis and anticoagulation, Blood. 135 (2020) 2033–2040, https://doi.org/10.1182/blood.2020006000.
[18] G. Chen, D. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, T. Wang, X. Zhang, H. Chen, H. Yu, X. Zhang, M. Zhang, S. Wu, J. Song, T. Chen, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical and immunological features of severe and moderate coronavirus disease 2019, J. Clin. Invest. 130 (2020) 2620–2629, https://doi.org/10.1172/JCI137244.
[19] B.R. Branchford, S.L. Carpenter, The role of inflammation in venous thromboembolism, Front. Pediatr. 6 (2018) 142, https://doi.org/10.3389/fped.2018.00142.
[20] C.L. Carty, P. Heagerty, S.R. Heckbert, G.P. Jarvik, L.A. Lange, M. Cushman, R. P. Tracy, A.P. Reiner, Interaction between fibrinogen and IL-6 genetic variants and associations with cardiovascular disease risk in the cardiovascular health study, Ann. Hum. Genet. 74 (2010) 1–10, https://doi.org/10.1111/j.1469-1809.2009.00551.x.
[21] D. Ragab, H.S. Eldin, M. Taeimah, R. Khattab, R. Salem, The COVID-19 cytokine storm; what we know so far, Front. Immunol. 11 (2020) 1446, https://doi.org/10.3389/fimmu.2020.01446.
[22] T. Omland, C. Prebensen, R. Røysland, S. Søvik, V. Sørensen, H. Røsjø, M. Svensson, J.E. Berdal, P.L. Myhre, Established cardiovascular biomarkers provide limited

prognostic information in unselected patients hospitalized with COVID-19, Circulation. 142 (2020) 1878–1880, https://doi.org/10.1161/CIRCULATIONAHA.120.050089.
[23] L.Y.C. Chen, R.L. Hoiland, S. Stukas, C.L. Wellington, M.S. Sekhon, Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome, Eur. Respir. J. 56 (2020), https://doi.org/10.1183/13993003.03006-2020.
[24] Y. Zaid, F. Puhm, I. Allaeys, A. Naya, M. Oudghiri, L. Khalki, Y. Limami, N. Zaid, K. Sadki, R.B.E. Haj, W. Mahir, L. Belayachi, B. Belefquih, A. Benouda, A. Cheikh, M.A. Langlois, Y. Cherrah, L. Flamand, F. Guessous, E. Boilard, Platelets can associate with SARS-CoV-2 RNA and are hyperactivated in COVID-19, Circ. Res. 127 (2020) 1404–1418, https://doi.org/10.1161/CIRCRESAHA.120.317703.
[25] B.K. Manne, F. Denorme, E.A. Middleton, I. Portier, J.W. Rowley, C.J. Stubben, Platelet gene expression and function in COVID-19 patients, Blood (2020), https://doi.org/10.1182/blood.2020007214 [published online ahead of print].
[26] Y. Wu, Contact pathway of coagulation and inflammation, Thromb. J. 13 (2015) 17, https://doi.org/10.1186/s12959-015-0048-y.
[27] M. Koupenova, H.A. Corkrey, O. Vitseva, G. Manni, C.J. Pang, L. Clancy, C. Yao, J. Rade, D. Levy, J.P. Wang, R.W. Finberg, E.A. Kurt-Jones, J.E. Freedman, The role of platelets in mediating a response to human influenza infection, Nat. Commun. 10 (2019) 1780, https://doi.org/10.1038/s41467-019-09607-x.
[28] A.J.G. Jansen, T. Spaan, H.Z. Low, D. Di Iorio, J. van den Brand, M. Tieke, A. Barendrecht, K. Rohn, G. van Amerongen, K. Stittelaar, W. Baumgärtner, A. Osterhaus, T. Kuiken, G.J. Boons, J. Huskens, M. Boes, C. Maas, E. van der Vries, Influenza-induced thrombocytopenia is dependent on the subtype and sialoglycan receptor and increases with virus pathogenicity, Blood Adv. 4 (2020) 2967–2978, https://doi.org/10.1182/bloodadvances.2020001640.
[29] M.A. Tortorici, A.C. Walls, Y. Lang, C. Wang, Z. Li, D. Koerhuis, G.J. Boons, B. J. Bosch, F.A. Rey, R.J. de Groot, D. Veesler, Structural basis for human coronavirus attachment to sialic acid receptors, Nat. Struct. Mol. Biol. 26 (2019) 481–489, https://doi.org/10.1038/s41594-019-0233-y.
[30] C.H. Kim, SARS-CoV-2 evolutionary adaptation toward host entry and recognition of receptor O-acetyl sialylation in virus-host interaction, Int. J. Mol. Sci. 21 (2020) 4549, https://doi.org/10.3390/ijms21124549.
[31] Y. Zuo, S. Yalavarthi, H. Shi, K. Gockman, M. Zuo, J.A. Madison, C. Blair, A. Weber, B.J. Barnes, M. Egeblad, R.J. Woods, Y. Kanthi, J.S. Knight, Neutrophil extracellular traps (NETs) in COVID-19, JCI Insight 5 (2020), https://doi.org/10.1101/2020.04.09.20059626. Preprint.
[32] C. Mozzini, D. Girelli, The role of neutrophil extracellular traps in Covid-19: only an hypothesis or a potential new field of research? Thromb. Res. 191 (2020) 26–27, https://doi.org/10.1016/j.thromres.2020.04.031.
[33] B.M. Henry, J. Vikse, S. Benoit, E.J. Favaloro, G. Lippi, Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: a novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis, Clin. Chim. Acta 507 (2020) 167–173, https://doi.org/10.1016/j.cca.2020.04.027.
[34] C. Ducroux, L. Di Meglio, S. Loyau, S. Delbosc, W. Boisseau, C. Deschildre, M. Ben Maacha, R. Blanc, H. Redjem, G. Ciccio, S. Smajda, R. Fahed, J.B. Michel, M. Piotin, L. Salomon, M. Mazighi, B. Ho-Tin-Noe, J.P. Desilles, Thrombus neutrophil extracellular traps content impair tPA-induced thrombolysis in acute ischemic stroke, Stroke. 49 (2018) 754–757, https://doi.org/10.1161/STROKEAHA.117.019896.
[35] I. Varjú, C. Longstaff, L. Szabó, A.Z. Farkas, V.J. Varga-Szabó, A. Tanka-Salamon, R. Machovich, K. Kolev, DNA, histones and neutrophil extracellular traps exert anti-fibrinolytic effects in a plasma environment, Thromb. Haemost. 113 (2015) 1289–1298, https://doi.org/10.1160/TH14-08-0669.
[36] Y. Zuo, M. Warnock, A. Harbaugh, S. Yalavarthi, K. Gockman, M. Zuo, J. A. Madison, J.S. Knight, Y. Kanthi, D.A. Lawrence, 2020, Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID-19 patients, medRxiv (2020), https://doi.org/10.1101/2020.08.29.20184358.
[37] J.N. Seheult, A. Seshadri, M.D. Neal, Fibrinolysis shutdown and thrombosis in severe COVID-19, J. Am. Coll. Surg. 231 (2020) 203–204, https://doi.org/10.1016/j.jamcollsurg.2020.05.021.
[38] T. Iba, J.H. Levy, T.E. Warkentin, J. Thachil, T. van der Poll, M. Levi, Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation, J. Thromb. Haemost. 17 (2019) 1989–1994, https://doi.org/10.1111/jth.14578.
[39] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, N. Kucher, J.D. Studt, C. Sacco, B. Alexia, M.T. Sandri, S. Barco, Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thromb. Res. 191 (2020) 9–14, https://doi.org/10.1016/j.thromres.2020.04.024.
[40] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemost. 18 (2020) 844–847, https://doi.org/10.1111/jth.14768.
[41] J. Helms, C. Tacquard, F. Severac, I. Leonard-Lorant, M. Ohana, X. Delabranche, H. Merdji, R. Clere-Jehl, M. Schenck, F.F. Gandet, S. Fafi-Kremer, V. Castelain, F. Schneider, L. Grunebaum, E. Anglés-Cano, L. Sattler, P.M. Mertes, F. Meziani, High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study, Intensive Care Med. 46 (2020) 1089–1098, https://doi.org/10.1007/s00134-020-06062-x.
[42] F. Marongiu, E. Grandone, D. Barcellona, Pulmonary thrombosis in 2019-nCoV pneumonia? J. Thromb. Haemost. 18 (2020) 1511–1513, https://doi.org/10.1111/jth.14818.
[43] N. Tang, Response to 'Pulmonary thrombosis in 2019-nCoV pneumonia?', J. Thromb. Haemost. 18 (2020) 1513–1514, https://doi.org/10.1111/jth.14843.
[44] F.B. Belen-Apak, F. Sarıalioğlu, Pulmonary intravascular coagulation in COVID-19: possible pathogenesis and recommendations on anticoagulant/thrombolytic therapy, J. Thromb. Thrombolysis 50 (2020) 278–280, https://doi.org/10.1007/s11239-020-02129-0.
[45] E. Gavriilaki, R.A. Brodsky, Severe COVID-19 infection and thrombotic microangiopathy: success doesn't come easily, Br. J. Haematol. 189 (2020) 227–230, https://doi.org/10.1111/bjh.16783.
[46] K. Hess, R. Ajjan, F. Phoenix, J. Dobó, P. Gál, V. Schroeder, Effects of MASP-1 of the complement system on activation of coagulation factors and plasma clot formation, PLoS One 7 (2012), e35690, https://doi.org/10.1371/journal.pone.0035690.
[47] A. Krarup, R. Wallis, J.S. Presanis, P. Gál, R.B. Sim, Simultaneous activation of complement and coagulation by MBL-associated serine protease 2, PLoS One 2 (2007), e623, https://doi.org/10.1371/journal.pone.0000623.
[48] J. Dobó, V. Schroeder, L. Jenny, L. Cervenak, P. Závodszky, P. Gál, Multiple roles of complement MASP-1 at the interface of innate immune response and coagulation, Mol. Immunol. 61 (2014) 69–78, https://doi.org/10.1016/j.molimm.2014.05.013.
[49] T.J. Guzik, S.A. Mohiddin, A. Dimarco, V. Patel, K. Savvatis, F.M. Marelli-Berg, M. S. Madhur, M. Tomaszewski, P. Maffia, F. D'Acquisto, S.A. Nicklin, A.J. Marian, R. Nosalski, E.C. Murray, B. Guzik, C. Berry, R.M. Touyz, R. Kreutz, D.W. Wang, D. Bhella, O. Sagliocco, F. Crea, E.C. Thomson, I.B. McInnes, COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options, Cardiovasc. Res. 116 (2020) 1666–1687, https://doi.org/10.1093/cvr/cvaa106.
[50] G. Tersalvi, M. Vicenzi, D. Calabretta, L. Biasco, G. Pedrazzini, D. Winterton, Elevated troponin in patients with coronavirus disease 2019: possible mechanisms, J. Card. Fail. 26 (2020) 470–475, https://doi.org/10.1016/j.cardfail.2020.04.009.
[51] M. Bansal, Cardiovascular disease and COVID-19, Diabetes Metab. Syndr. 14 (2020) 247–250, https://doi.org/10.1016/j.dsx.2020.03.013.
[52] N.E. Ingraham, A.G. Barakat, R. Reilkoff, T. Bezdicek, T. Schacker, J.G. Chipman, C.J. Tignanelli, M.A. Puskarich, Understanding the renin-angiotensin-aldosterone-SARS-CoV-axis: a comprehensive review, Eur. Respir. J. 56 (2020), https://doi.org/10.1183/13993003.00912-2020.
[53] R. Cheng, D. Leedy, COVID-19 and acute myocardial injury: the heart of the matter or an innocent bystander? Heart. 106 (2020) 1122–1124, https://doi.org/10.1136/heartjnl-2020-317025.
[54] P. Wenzel, S. Kopp, S. Göbel, T. Jansen, M. Geyer, F. Hahn, K.F. Kreitner, F. Escher, H.P. Schultheiss, T. Münzel, Evidence of SARS-CoV-2 mRNA in endomyocardial biopsies of patients with clinically suspected myocarditis tested negative for COVID-19 in nasopharyngeal swab, Cardiovasc. Res. 116 (2020) 1661–1663, https://doi.org/10.1093/cvr/cvaa160.
[55] B. Siripanthong, S. Nazarian, D. Muser, R. Deo, P. Santangeli, M.Y. Khanji, L. T. Cooper Jr., C.A.A. Chahal, Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management, Heart Rhythm. S1547-5271 (2020) 30422–30427, https://doi.org/10.1016/j.hrthm.2020.05.001.
[56] A.R. Fatkhullina, I.O. Peshkova, E.K. Koltsova, The role of cytokines in the development of atherosclerosis, Biochemistry (Mosc) 81 (2016) 1358–1370, https://doi.org/10.1134/S0006297916110134.
[57] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, C. Clark, T. Iba, ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J. Thromb. Haemost. 18 (2020) 1023–1026, https://doi.org/10.1111/jth.14810.
[58] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet. 395 (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.
[59] L. Zhang, X. Yan, Q. Fan, H. Liu, X. Liu, Z. Liu, Z. Zhang, D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19, J. Thromb. Haemost. 18 (2020) 1324–1329, https://doi.org/10.1111/jth.14859.
[60] X. Yang, Q. Yang, Y. Wang, Y. Wu, J. Xu, Y. Yu, Y. Shang, Thrombocytopenia and its association with mortality in patients with COVID-19, J. Thromb. Haemost. 18 (2020) 1469–1472, https://doi.org/10.1111/jth.14848.
[61] A. Amgalan, M. Othman, Exploring possible mechanisms for COVID-19 induced: thrombocytopenia unanswered questions, J. Thromb. Haemost. 18 (2020) 1514–1516, https://doi.org/10.1111/jth.14832.
[62] N. Morelli, E. Rota, C. Terracciano, P. Immovilli, M. Spallazzi, D. Colombi, D. Zaino, E. Michieletti, D. Guidetti, The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 era, Eur. Neurol. 83 (2020) 213–215, https://doi.org/10.1159/000507666.
[63] V. Pavoni, L. Gianesello, M. Pazzi, C. Stera, T. Meconi, F.C. Frigieri, Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia, J. Thromb. Thrombolysis 50 (2020) 281–286, https://doi.org/10.1007/s11239-020-02130-7.
[64] J. Rello, E. Storti, M. Belliato, R. Serrano, Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers, Eur. Respir. J. 55 (2020) 2001028, https://doi.org/10.1183/13993003.01028-2020.
[65] W.J. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, J. Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Y. Hu, P. Peng, J. Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, N. Zhong, Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720, https://doi.org/10.1056/NEJMoa2002032.
[66] M. Panigada, N. Bottino, P. Tagliabue, G. Grasselli, C. Novembrino, V. Chantarangkul, A. Pesenti, F. Peyvandi, A. Tripodi, Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings

and other parameters of hemostasis, J. Thromb. Haemost. 18 (2020) 1738–1742, https://doi.org/10.1111/jth.14850.
[67] L. Roncon, M. Zuin, P. Zonzin, Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in COVID-19 patients, Thromb. Res. 190 (2020) 102, https://doi.org/10.1016/j.thromres.2020.04.021.
[68] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, H. Wang, J. Wan, X. Wang, Z. Lu, Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) 1–8, https://doi.org/10.1001/jamacardio.2020.1017.
[69] A. Ciavarella, F. Peyvandi, I. Martinelli, Where do we stand with antithrombotic prophylaxis in patients with COVID-19? Thromb. Res. 191 (2020) 29, https://doi.org/10.1016/j.thromres.2020.04.023.
[70] J.F. Llitjos, M. Leclerc, C. Chochois, J.M. Monsallier, M. Ramakers, M. Auvray, K. Merouani, High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients, J. Thromb. Haemost. 18 (2020) 1743–1746, https://doi.org/10.1111/jth.14869.
[71] C.D. Barrett, H.B. Moore, M.B. Yaffe, E.E. Moore, ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment, J. Thromb. Haemost. 18 (2020) 2060–2063, https://doi.org/10.1111/jth.14860.
[72] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Levi, C. Clark, T. Iba, M. Cattaneo, Type and dose of heparin in Covid-19: reply, J. Thromb. Haemost. 18 (2020) 2063–2064, https://doi.org/10.1111/jth.14870.
[73] Z. Zhai, C. Li, Y. Chen, G. Gerotziafas, Z. Zhang, J. Wan, P. Liu, I. Elalamy, C. Wang, Prevention and treatment of venous thromboembolism associated with coronavirus disease 2019 infection: a consensus statement before guidelines, Thromb. Haemost. 120 (2020) 937–948, https://doi.org/10.1055/s-0040-1710019.
[74] J. Thachil, The versatile heparin in COVID-19, J. Thromb. Haemost. 18 (2020) 1020–1022, https://doi.org/10.1111/jth.14821.
[75] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, J. Thromb. Haemost. 18 (2020) 1094–1099, https://doi.org/10.1111/jth.14817.
[76] L. Omarjee, O. Meilhac, F. Perrot, A. Janin, G. Mahe, Can ticagrelor be used to prevent sepsis-induced coagulopathy in COVID-19? Clin. Immunol. 216 (2020) 108468, https://doi.org/10.1016/j.clim.2020.108468.
[77] E. Akşit, B. Kırılmaz, E. Gazi, F. Aydın, Ticagrelor can be an important agent in the treatment of severe COVID-19 patients with myocardial infarction, Balkan Med. J. 37 (2020) 233, https://doi.org/10.4274/balkanmedj.galenos.2020.2020.4.100.