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Review

Emerging patterns of hypercoagulability associated with critical COVID-19: A review

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ABSTRACT

While the COVID-19 pandemic sweeps the world, much evidence is being gathered regarding its novel pathological mechanisms. It is the authors' clinical experience that patients in the intensive care unit suffering from COVID-19 are extremely pro-coagulable, with venous and arterial thromboembolism frequently observed, and losses of vascular access lines and filtration circuits to thrombosis now commonplace. Here, we explore the evidence for hypercoagulability in this group, presenting evidence of both a localised pulmonary hypercoagulability, and a systemic hypercoagulability resulting in thrombosis distant to the pulmonary vasculature. Furthermore, we discuss the possible risk factors exacerbated by, or selected for in COVID-19. We review the available evidence for use of plasma D-dimer as a prognostic marker, exploring the possibility that it acts as a marker of a COVID-19-associated hypercoagulability. We review the evidence for a pro-coagulant subtype of disseminated intravascular coagulation, discussing its clinical significance. Finally, we discuss the current evidence surrounding treatment of COVID-19 hypercoagulability, including prophylactic and treatment-dose heparin, thrombolytic agents, antiplatelet agents, and direct thrombin inhibitors, among others. We suggest areas in which further investigation is urgently needed to reduce the startling incidence of thrombosis in this group, a complication no doubt contributing to morbidity and mortality.

Contents

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1. Introduction

The novel human coronavirus SARS-Cov2, which causes the clinical syndrome termed COVID-19, first emerged in Wuhan, China in December 2019. It has since caused a pandemic with devastating global consequences, infecting more than 10 million and causing over 500,000 deaths to date [1]. The clinical course is primarily a fever, dry cough and myalgia, progressing in 10–15% to a viral pneumonia and type 1 respiratory failure (defined as hypoxaemia without hypercapnia), with roughly a third of patients requiring intensive care unit (ICU) admission with an atypical acute respiratory distress syndrome (ARDS) [2], sometimes with multi-system involvement [3]. The authors' clinical experience is that patients with COVID-19 are extremely pro-coagulable, with frequent losses of critical care lines, haemofiltration circuits, and abnormally frequent thromboembolic disease. Abnormal coagulation laboratory results in COVID-19 are associated with poor prognosis and disseminated intravascular coagulation (DIC) is frequent in patients with fatal outcomes [4]. Evidence for therapeutic strategies continues to emerge, but few randomised controlled trials exist.

2. Evidence for hypercoagulability in COVID-19

2.1. Macrovascular thromboembolism

Macrovascular complications appear common in critical COVID-19, with several reports in the literature [5,6]. Retrospective analysis of lower limb ultrasound scans of 81 COVID-19 patients admitted to one ICU in Wuhan revealed a 25% incidence of deep vein thrombosis (DVT), correlating with increased plasma D-dimer [7]. Frequency of scans was not disclosed, and no patient in the study was given low molecular-weight heparin (LMWH). A death rate of just 4% was reported, markedly lower than would be expected in an ICU population in the UK, suggesting different admission criteria. The first robust observational data in critical COVID-19 patients was provided by a prospective study in three Dutch centres, which found a 27% incidence of venous thromboembolism (VTE) and 3.7% incidence of arterial thrombosis in 184 patients during a one month period, despite prophylactic anticoagulation [8]. A retrospective study of 69 ICU patients at Addenbrooke's hospital, UK, revealed similar results [9]. Middeldorp et al. conducted an observational study of 198 COVID-19 patients hospitalised in a single centre in the Netherlands, 75 of whom were admitted to ICU for mechanical ventilation [10]. Clinical suspicion of VTE prompted investigation, revealing a 20% incidence despite prophylaxis (and double prophylaxis in some cases). Risk of VTE increased over time, and was associated with mortality. Patients admitted to ICU had dramatically higher incidence of VTE than ward-based patients at all timepoints during the 21 day follow-up period (day 21: 59% vs. 9.2%), although therapeutic anticoagulation appeared protective. A similar study of 388 consecutive patients with COVID-19 in Milan, Italy revealed VTE, stroke, or myocardial infarction in 27.6% of ICU patients and 6.6% of ward patients investigated on clinical suspicion, despite thromboprophylaxis in all ICU patients (16%), and 75% of ward patients [11]. Helms et al. prospectively studied 150 patients admitted to four ICUs in France with ARDS due to COVID-19 [12]. Although some patients were followed up for as little as 7 days, 16.7% developed PEs, 96.6% of 29 patients treated with haemofiltration had a circuit clot, and of 1 of the 12 patients who received extracorporeal membrane oxygenation (ECMO) suffered from a centrifugal pump thrombotic occlusion. Of 100 CTPAs performed in 99 patients, 25% were positive for PE. Ischaemic or haemorrhagic stroke was present in 4 of 25 patients who underwent brain imaging. One autopsy series has even revealed DVT in 58% of its 12 COVID-19 patients, none of whom were suspected to have DVT before death [13].

While arterial thrombosis is not typically considered a feature of sepsis or infection, it is unexpectedly prominent in COVID-19; there are reports of acute limb ischaemia [14] and even mesenteric ischaemia [15]. An increased prevalence of ischaemic stroke in patients affected by respiratory viruses has been noted previously [16,17]. In a retrospective study of 216 patients in Wuhan, severe COVID-19 was associated with increased incidence of cerebrovascular disease, with four ischaemic and one haemorrhagic stroke in the in the severe group (5.7%), versus one case (0.8%) in the non-severe group, although 7.0% of patients had existing cerebrovascular disease [18]. A systematic review of early studies from China noted that the combined incidence of stroke (2.2%) was similar to the background incidence in the Chinese population, although the co-presence of stroke and COVID-19 had an associated three-fold risk of death [19]. Several further studies in Europe have emerged. A research letter from Queen's Square, UK described six patients presenting with neurological symptoms in addition to COVID-19 who were eventually diagnosed with acute stroke on brain imaging [20]. Interestingly, three patients had multi-territory infarction, and two suffered stroke despite therapeutic anticoagulation. The mean range of presentation was 8–24 days after COVID-19 symptom onset, although one patient developed stroke while still asymptomatic from COVID-19. Thrombotic stroke has been reported in patients suffering from even mild COVID-19 [21]. An observational study in France has revealed incidentally detected ischaemic stroke in 3 of 13 COVID-19 patients (23%) who underwent MRI head due to unexplained encephalopathic symptoms [22]. One group in New York City, USA, reported 5 patients under 50 years presenting with COVID-19 and large-vessel ischaemic stroke during a two week period in March–April 2020, calculating that every two weeks from the previous 12 months, 0.73 patients in this age group would present similarly [23]. However, since only a single fortnight period during the pandemic is reported, this may represent statistical anomaly. One further paper by Li et al. [24] has been extensively cited [25], including in the conclusions of an 18 country international panel of stroke experts [26], although the paper is now no longer available.

2.2. Pulmonary microvascular thrombosis

There is increasing evidence that pulmonary clots as a result of COVID-19 may not represent straightforward embolic disease. The relative frequency of PE in the absence of DVT in COVID-19 has been noted by several authors [8,27,28]. Furthermore, one group note their empirical observation that thrombosis-in-situ is the prominent pattern on angiographic lung imaging, with appearances typical for non-occlusive thrombi rather than emboli, which tend to fully occlude the vessels in which they lodge [27]. Others have observed that in some patients with COVID-19 ARDS the degree of lung compliance is preserved disproportionately given the degree of hypoxia, possibly suggesting a shunting mechanism as an explanation for the hypoxia [29,30]. Indeed, right ventricular dilatation was observed in one autopsy series of COVID-19 patients [31], and some suggest the raised troponin observed frequently in COVID-19 is as a result of pulmonary hypertension [32].There is even some evidence of shunt from lung perfusion imaging [33], although the authors suggest that the observed patterns may be atypical for pulmonary thrombosis.

Autopsy reports provide further evidence of pulmonary thrombosis. Fibrin deposition and formation of micro-emboli is evident within the lungs and elsewhere at autopsy [31,34], and microthrombi rich in platelets and fibrin have been observed [35]. Features in one series were reported consistent with a thrombotic microangiography restricted to the lungs [31]. Some autopsy series report pulmonary microthrombosis and even infarction despite anticoagulation [36,37]. Similar findings are reported in Severe Acute Respiratory Syndrome (SARS) [38] and Middle Eastern Respiratory Syndrome (MERS) [39], although microthrombi were reportedly less likely to present in patients who died of influenza [40]. One group has suggested based on autopsy that COVID-19 represents a complement-mediated microvascular angiopathy, explaining both the lung manifestations and the purpuric skin rash observed in some patients [41].

The mechanism of this pulmonary thrombosis syndrome remains under debate [32]. One group has suggested that the hypercoagulability observed in critical COVID-19 may represent a localised DIC confined to the lungs [42], making reference to their previous paper proposing that pulmonary thrombosis, as a separate clinical entity to pulmonary embolism, may underlie the pathogenesis of pneumonia, asthma and chronic obstructive pulmonary disease through a close relationship between local inflammation and coagulation promoting fibrin deposition in the lungs [43]. Existing theories regarding the pathogenesis of ARDS hypothesise that activation of the pulmonary endothelium results in inflammation leading to microthrombi [44–46]. Some have argued that while heparin is indeed protective against VTE in patients with COVID-19, it may do nothing to protect against in-situ pulmonary microvascular thrombosis [27]. However, nebulised anticoagulant therapy has been previously proposed as a treatment of ARDS [47]. Thus, there may be two distinct subtypes of ARDS in COVID-19: typical ARDS due to alveolar oedema and damage resulting in reduced lung compliance, and atypical ARDS due to localised pulmonary microthrombi resulting in profound hypoxia with preserved lung compliance.

2.3. Risk factors for hypercoagulability in COVID-19

Investigation of hypercoagulability in COVID-19 is confounded by associated risk factors. Both hypertension and diabetes appear more frequently in patients with COVID-19 [48], and are also risk factors for hypercoagulability [49,50]. Critical care admission is itself a risk factor for VTE, with incidence of 13–31% reported in the absence of anticoagulation [51] and an incidence of 7.7% despite prophylactic anticoagulation [52], jumping dramatically to 37% in sepsis [53]. Mechanical ventilation is a further risk factor [53,54], as is hypoxia, which promotes hypercoagulability even in healthy volunteers [55]. ARDS management strategies appear to further compound this risk, with both negative fluid balance and high positive end-expiratory pressure (PEEP) increasing risk of VTE [56–58]. COVID-19 patients were initially managed with extremely high PEEP; it is thought that compression of the great veins within the chest increases venous stasis, and thus promotes DVT [57]. There are further hints that COVID-19 itself amplifies the hypercoagulability associated with these risk factors; 77 patients with ARDS due to COVID-19 were matched with 145 patients with ARDS due to other viral or bacterial infection, finding significantly more thrombotic complications in COVID-19 ARDS than ARDS from other causes (11.7% vs. 4.8%, $p = 0.035$), with PE predominating [12]. Interestingly, while the series reported significantly lower D-dimer in COVID-19 ARDS, the incidence of thrombotic events was higher. The intense inflammatory response observed in patients with COVID-19 even in the absence of severe respiratory symptoms further increases their risk of thrombotic disease [59]. Outside of critical care, normally mobile individuals obeying stay-at-home orders may be at increased risk of VTE through immobility, with some authors suggesting extended prophylaxis on discharge for COVID-19 patients at high risk of VTE may be reasonable [60]. Late presentation to hospital with other pathology during the pandemic results in patients who would otherwise present to hospital and be treated with prophylactic anticoagulation instead remaining at home, thereby increasing risk of thrombosis.

3. D-dimer in COVID-19

In health, haemostasis is carefully balanced between formation of fibrin clots in response to vascular injury, and clot breakdown via the fibrinolytic pathway. D-dimers are formed when plasmin cleaves fibrin as part of this fibrinolytic pathway, and are detectable approximately 2 h after index thrombus formation [61]. Due to high sensitivity of the assay, D-dimer in clinical practice has evolved from primarily screening for DIC, to exclusion of VTE. The test is nonspecific, however, with any inflammatory condition potentially causing elevated D-dimer.

3.1. D-dimer is prognostic in COVID-19

Predictably, initial epidemiological descriptive data has demonstrated elevated D-dimer levels in COVID-19 pneumonia [62]. However, unfolding data is providing insight into the utility of D-dimer for prognostication and monitoring disease progress. A retrospective study analysed 183 consecutive hospitalised COVID-19 patients, revealing a statistically significantly raised admission D-dimer in patients with fatal outcome when compared to survivors (2120 μg/L [770–5270] vs. 610 μg/L [350–1290]) [4]. Although many patients exhibited multiple pro-coagulant comorbidities, these did not differ significantly between outcome groups. A further observational study of 191 COVID-19 patients in Wuhan revealed that an admission D-dimer above 1000 μg/L was present in 81% of non-survivors, and just 42% of survivors [48]. However, the study terminated at a set date, and stratified patients based on status at study termination, rather than following up to outcome. Yao et al. found that D-dimer value correlated with increased clinical severity (Kendall's tau 0.374), reporting a sensitivity of 88.2% and specificity of 71.3% of a D-dimer of above 2140 μg/L for in-hospital mortality. A prospective series of 41 patients in Wuhan found those requiring ICU admission to have statistically significantly higher D-dimer than non-critical cases (2400 μg/L [600–14,400] vs. 500 μg/L [300–800]) [63]; this has been replicated in a further retrospective series of 138 patients, with the

study also finding that further increase in plasma D-dimer over time correlated with mortality [64]. D-dimer has been found to correlate with severity of COVID-19 even in milder cases, with a reported association between increased D-dimer and progression to ARDS, as well as progression of ARDS to mortality [65]. It is interesting that the only study to collect data from patients not admitted to hospital resulted in lower D-dimer values overall: in 260 patients with laboratory-confirmed COVID-19 (both hospital inpatients and outpatients), 41% had an initial D-dimer above 500 μg/L, although this rose to 59.6% in patients with severe disease [66]. It is, therefore, abundantly clear that D-dimer correlates with severity of disease and mortality in COVID-19. The question remains, however, whether D-dimer simply acts as an acute phase marker, declaring the severity of infection, or it represents a distinct hypercoagulability in the pathogenesis of COVID-19.

3.2. D-dimer as an acute phase marker

Given the role of fibrin formation in the inflammatory response, and the intensive inflammation associated with ARDS, the elevation of plasma D-dimer in COVID-19 may be argued to be a result of the acute phase response rather than a marker of a separate hypercoagulability. The immunothrombosis model proposes that inflammation and coagulation are inextricably linked [67]; fibrin has been theorised to act as an effector arm of the immune system by trapping the invading pathogen. Alveolar fibrin deposition is absent in health, but is a hallmark of diffuse alveolar damage and acute lung injury (ALI) [68]. The coagulation and immune systems together cause endothelial dysfunction [69], and inflammatory mediators also increase local expression of tissue factor and thereby facilitate formation of fibrin both intra- and extravascularly. Macrophages are prominent in ARDS and in COVID-19 [70], and contribute to formation of D-dimers both by phagocytosis and lysosomal digestion of fibrin, and by production of urokinase to allow movement through the extracellular matrix [71]. Thus, the correlation of increasing D-dimer and mortality from COVID-19 may simply reflect quantity of activated macrophages and inflammatory burden within the lungs.

3.3. D-dimer as marker of hypercoagulability

Based on the observational data, we theorise that D-dimer is at least in part a marker of hypercoagulability when measured in the context of COVID-19. While D-dimer has indeed been shown previously to correlate with poorer outcomes even in simple bacterial pneumonia [72], Yin et al. re-analysed data from Tang et al. [4] and matched 449 patients with severe COVID-19 pneumonia against 104 with non-COVID pneumonia admitted earlier in the year. Although they demonstrated elevated D-dimer in both groups, and no significant difference between them, treatment-dose LMWH compared to no anticoagulation improved survival in patients with a D-dimer over 6 times the upper limit of normal in only the COVID-19 group [73]. In fact, the magnitude of the survival advantage increased with an increasing D-dimer in patients with COVID-19, while the non-COVID-19 pneumonia group received no survival advantage from LMWH even with high plasma D-dimer. Although the strict definition of ARDS was not used, the non-COVID-19 pneumonia group exhibited several of the criteria used in the Berlin ARDS classification, thus rendering the groups comparable. In an interesting study, Cui et al. retrospectively analysed 81 COVID-19 patients on ICU, none of whom were anticoagulated, finding that 25% had a DVT detectable on ultrasound, and that a D-dimer cutoff of 1500 μg/L resulted in a 85% sensitivity and 88.5% specificity for DVT, with a 94.7% negative predictive value [7]. Risk of DVT in this group was clearly associated with raised D-dimer.

3.4. D-dimer as a marker of comorbidity/pre-inflammatory state

In the absence of any infection, plasma D-dimer is known to correlate with atherosclerotic burden [74], and is elevated in patients type 2 diabetes compared to non-diabetics, particularly in the presence of vascular complications [75]. It is interesting, therefore, that in 174 patients suffering from COVID-19, a statistically significant elevation in D-dimer was observed in the subset of diabetic patients compared to non-diabetics [76]. The authors argue that diabetic patients are more susceptible to rapid deterioration from COVID-19 secondary to an inflammatory storm reflected by the D-dimer.

4. Disseminated intravascular coagulation

DIC is an acquired syndrome characterised by widespread activation of the coagulation cascade and mass consumption of clotting factors. It is caused by activation of tissue factor resulting in hypercoagulability, with concomitant suppression of fibrinolysis by upregulation of plasminogen activator inhibitor 1 (PAI-1) [77], among others. Overall, this results in endothelial dysfunction, microvascular thrombosis, and microcirculatory stasis leading to multi-organ failure [78], followed by bleeding as coagulation factors are depleted. While there is no single diagnostic test for DIC, an International Society of Thrombosis and Haemostasis (ISTH) diagnostic scoring system exists [79] involving platelet count [80], prothrombin time (PT) [81], fibrinogen level, and D-dimer.

While robust evidence for classical DIC in COVID-19 is lacking, it has been observed in SARS, with one study reporting a 2.5% incidence [82]. Autopsy reports of three patients with COVID-19 have revealed presence of hyaline microthrombi throughout organ systems without direct viral infection of adjacent cells, suggesting a systemic hypercoagulability [70]. Reports of PT prolongation in COVID-19 again hint towards the presence of DIC in these patients; this has been observed in COVID-19 patients requiring ICU compared with those who did not (12.2 s vs. 10.7 s, $p = 0.012$) [83], who developed ARDS compared with those who did not (11.7 s vs. 10.0 s, $p < 0.001$) [65], and in non-survivors compared with survivors (15.5 s vs. 13.6 s, $p < 0.001$) [4]. In addition, Tang et al. demonstrated elevated FDPs, and a marked divergence in levels of fibrin and antithrombin in COVID-19 survivors versus non-survivors as the illness progressed [4]. 71.4% of non-survivors in their study reached the ISTH diagnostic criteria for DIC, compared to 0.6% of survivors, and median time to develop DIC was 4 days from admission (range 1–12 days). In another study, 2.2% of 288 COVID-19 patients developed overt DIC (half of whom had malignancy), resulting in an 88% mortality [11]. This compares with a reported mortality of 54.7% from DIC due to other causes [84].

However, this COVID-19-induced DIC appears different to that of classical DIC seen in fulminant sepsis. Firstly, classical DIC is often seen in the clinical context of hypotension, tachycardia, and lactatemia, none of which are prominent features of COVID-19 [3]. Secondly, the profound bleeding associated with classical DIC does not appear to be a feature [85], though patients often present with markedly decreased fibrinogen levels and elevated levels of FDPs [86]. Indeed while heparin is usually avoided in DIC, it appears beneficial in COVID-19 [8]. Thus, it would appear that these patients suffer from an unusual hypercoagulable form of DIC [87]. Some authors have even suggested that this atypical DIC contributes to COVID-19 mortality independent of ARDS, given the fact that elevated D-dimer seems to predict mortality to a greater degree than development of ARDS itself [88]. Thus, the ISTH recommends routine measurement of fibrinogen in critical COVID-19, and the reporting of DIC score on all results returned in these patients [89].

5. Platelets

Thrombocytopenia (typically defined as platelet count below 150 × 109 per litre [90]) has long featured in critical illness prognostic scores [91–93], and is known to correlate with disease severity and mortality in ICU [94–96]. This is likely multifactorial, but is at least in part due to the often pre-terminal massive platelet activation and consumption seen in classical DIC. Thrombocytopenia was reported in up to 55% of patients with SARS [97,98], and along with leukopenia was the most prominent laboratory finding [99]. A SARS prognostic model used only the degree of hypoxaemia and thrombocytopenia to estimate mortality with an impressive 96.2% accuracy [100]. Thrombocytopenia and lymphopenia were associated with development of pneumonia, respiratory failure, and overall disease severity in MERS [101,102]. A similar picture is now emerging in COVID-19, with thrombocytopenia present in 36.2% of laboratory-confirmed COVID-19 patients in Wuhan [66], and a recent meta-analysis demonstrating that thrombocytopenia was associated with a greater than fivefold increased risk of severe illness [103]. Given the emerging picture of pulmonary microvascular thrombosis, and the reported higher platelet counts in some patients with COVID-19 [73], some authors have proposed two distinct phases of platelet response in COVID-19: stimulation of production of highly activated platelets in the early stage as a response to acute pulmonary inflammation [104,105], followed by sequestration in the pulmonary microvasculature. Thus, while thrombocytopenia appears to highlight severe disease, more work is required to examine the currently unclear pathological processes involved.

6. Therapeutic options

6.1. Heparin

Although prophylactic anticoagulation is standard of care in the UK, the relationship between high D-dimer and mortality has prompted the consideration of treatment-dose anticoagulation with heparin even in the absence of proven VTE. Heparin acts as an anticoagulant by binding antithrombin. However, beyond the coagulation cascade heparin is known to dampen inflammation through its interaction with key inflammatory mediators. Significantly reduced levels of IL-6 and higher lymphocyte counts have been observed in COVID-19 patients treated with heparin [106], a finding of particular interest given the evidence that IL-6 levels and the associated cytokine storm correlate with severity of COVID-19 [107].

6.1.1. Evidence supporting the use of prophylactic heparin

Tang et al. performed a retrospective study of 449 patients admitted to Tongji Hospital, Wuhan with COVID-19, comparing 99 patients who received LMWH (mainly enoxaparin 40–60 mg for at least 7 days) with 350 patients who received no heparin [86]. Although they found no survival benefit overall, anticoagulation with heparin was associated with reduced mortality in a dose-response effect as plasma D-dimer increased. A striking 20% survival benefit was seen with heparin in the 311 patients in whom plasma D-dimer was 3000 μg/L and above. However, incidence of VTE was unfortunately not reported, characteristics of patients in the anticoagulation and no-treatment groups were not compared, and the authors did not state indications for treatment among the 22% of patients given heparin. In addition, patients in the heparin group were recruited later to the study, possibly leading to performance bias when treating a novel disease. Patients in the comparator arm were not anticoagulated, in contrast to standard practice in the UK. The survival benefit of heparin appears to be peculiar to COVID-19 rather than any severe lung infection [73]. A multicenter retrospective study of all 2075 patients with COVID-19 admitted to 17 Spanish hospitals demonstrated a significantly reduced mortality in patients given heparin versus no anticoagulation (odds ratio 0.55, 95% CI 0.37–0.82, p = 0.003). While they did not report indications for treatment, doses, or duration, the observed effect was maintained when oxygen saturation, temperature, age, gender, and other treatments were accounted for by logistic regression [108].

6.1.2. Evidence supporting the use of treatment-dose heparin

Some have suggested that prophylactic anticoagulation may be insufficient to treat COVID-19 hypercoagulability [109], arguing that high levels of fibrinogen have been shown to reduce the efficacy of prophylactic-dose heparin [110]. Independent of COVID-19, a prophylactic LMWH failure rate of 12.5% over 30 days in patients admitted to ICU with sepsis has been observed, jumping to 31% in patients with ARDS [58]. Interestingly, the risk of VTE in ICU patients with COVID-19 was not reduced following doubling of prophylactic nadroparin in one study [10]. A 56% cumulative incidence of VTE was reported despite therapeutic anticoagulation in 18 ICU patients with severe COVID-19 [111]. A series of 15 critical COVID-19 patients in the UK treated with therapeutic heparin (for either confirmed VTE or to prevent filter thrombosis) reported that 80% of patients had 'heparin resistance' defined as requiring >35,000 units heparin per day for the APTT to be within range, and response to heparin in their in vitro assay was unexpectedly non-linear [112]. A preprint case series of 27 hospitalised COVID-19 patients in Brazil investigated a novel protocol of either enoxaparin 1 mg/kg once daily or unfractionated heparin (UFH) 5000 units every 6–8 h. Desaturation or increasing D-dimer prompted doubling of the dose, while thrombosis or worsening hypoxia prompted increase to enoxaparin 2 mg/kg twice daily. Improvement in oxygenation was observed following commencement of enoxaparin, and no bleeding complications were observed despite the high doses used [30].

6.1.3. Drawbacks of heparin treatment

Currently no data are available from randomised trials to assess the benefit of heparin in COVID-19, although other coagulopathies associated with critical illness have not benefited from anticoagulation [113]. Use of heparin generally is associated with a 10–15% risk of significant bleeding [114], which must be taken into account. One group reports that 11 centres in Italy referred a total of 38 patients with COVID-19 to a tertiary centre over a one month period with major bleeding following therapeutic heparin, 71% of whom were ICU patients [115]. Embolisation was considered in these cases due to the perceived drawbacks of termination of therapeutic heparin. Indeed 65.7% underwent lifesaving embolisation of a bleeding point, while in 34.2% it was considered safe to stop heparin (although 46.2% of these patients still required embolisation). Bleeding was primarily intramuscular, although some intracranial and intra-abdominal bleeding was observed. The authors cite concerns that formation of field hospitals without access to interventional radiology, and movement of infective patients between departments and centres, may have major consequences for patients and staff. Reassuringly, bleeding events seem to be reported infrequently in the observational studies, despite even high doses of heparin [30,86]. We eagerly await the results of the now numerous registered clinical trials involving heparin, including one specifically investigating nebulised heparin.

6.2. Thrombolysis

Thrombolytic drugs activate plasminogen to plasmin (a proteolytic enzyme which cleaves crosslinked fibrin), and are

commonly used following acute ischaemic stroke, PE with circulatory compromise, or other severely symptomatic thrombotic events.

6.2.1. Use of thrombolysis in COVID-19 in proven thrombosis

Concerns have been raised that attempting thrombolysis for acute ischaemic stroke in patients with COVID-19 may increase the risk of intracranial haemorrhage or death, given the previously observed trends in patients with infective endocarditis [116] and elevated inflammatory markers [117]. Current guidance still favours the use intravenous thrombolysis within the 3 h despite COVID-19 infection, but predicts that clinical improvements may be more limited [26]. Indeed, 5 patients underwent thrombolysis in a case series of 10 in Paris co-presenting with acute stroke and COVID-19, and all 10 subsequently underwent thrombectomy [118]. Although no patients experienced intracranial bleeding, 4 had cerebral reocclusion despite treatment. In-hospital mortality was 60%, with no clinical improvement amongst survivors. The potential uses of thrombolysis are even being extended during the COVID-19 crisis; one 50-year-old patient co-presenting with COVID-19 and low-to-intermediate risk saddle PE on chest imaging was treated with catheter-directed thrombolysis in the absence of right heart strain or haemodynamic compromise, resulting in clinical and radiological improvement [119]. No bleeding was reported, although the patient's overall clinical outcome was not disclosed.

6.2.2. Use of thrombolysis in COVID-19 outside of proven thrombosis

Given the alveolar fibrin deposition and pulmonary microthrombi in ARDS, thrombolysis has been explored as a 'salvage agent' in ARDS, even where there is no evidence of overt thrombus. A comprehensive meta-analysis of animal models of ALI reports that treatment with thrombolytic agents significantly improved gas exchange, lessened pulmonary oedema, and reduced alveolar neutrophil count and histologic severity of lung injury [120]. Tissue plasminogen activator (tPA) in particular was associated with a reduction in mortality compared with untreated controls. However, the 14 animal models did not include a virally-induced ARDS model, making the report of limited applicability to COVID-19. Two case series to date investigate this 'salvage therapy' option in patients with critical COVID-19. Wang et al. treated 3 ventilated COVID-19 patients with an intravenous alteplase loading dose, followed by a tPA infusion over 22 h, and then UFH at treatment dose [121]. They demonstrated striking initial improvement in oxygenation, but this was persistent in only one patient after completion of the infusion, and mortality remained high. A preprint series reports 4 cases of thrombolysis with tPA in COVID-19 ICU patients, resulting in improved alveolar ventilation on blood gasses in 3 patients, and reduced vasopressor requirement in 3 [122]. Two patients had not improved with treatment-dose anticoagulation, but demonstrated almost immediate physiological improvement upon administration of tPA. Overall outcome measures were not reported with the exception of one patient who suffered a cardiac arrest shortly after an initial improvement from thrombolysis, with large biventricular thrombi identified on echocardiography thought to be the likely cause of arrest.

Inhaled plasminogen appears to improve oxygenation according to a case series of 13 patients with COVID-19; in the moderately severe group, lung imaging appearances improved and there was a statistically significant decrease in heart rate, while 5 of 6 patients in the severe group had increases of oxygen saturations of 1–4% [123]. Oxygen saturations improved from around 79-82%–91% just an hour after treatment in both critical patients. It is likely that enhancing fibrinolysis within the alveolar space specifically promotes improved gas exchange by removal of deposited fibrin, thus reducing diffusion distance. In newborns suffering from ARDS secondary to hyaline membrane disease, circulating plasminogen levels are low, and supplementation has been shown to be effective in reducing mortality [124]. In healthy adults, however, the mechanism of this treatment remains unclear as plasminogen circulates in excess and is not thought to be rate-limiting.

Overall, current evidence for thrombolysis as 'salvage therapy' is limited. Moore et al. argue for its consideration as a compassionate treatment in patients suffering from COVID-19 ARDS with poor oxygenation and raised CO2 despite prone positioning and maximal mechanical ventilatory support, especially when ECMO is not available [125]. They argue for consideration of a prolonged infusion in COVID-19, rather than a one-off lytic treatment, due to the prolonged widespread disruption of the haemostatic system. Despite the 1% risk of catastrophic bleeding from tPA in non-stroke patients [126,127], no incidents of bleeding after thrombolysis in COVID-19 patients have been reported in the literature to date.

6.3. Antiplatelet agents

Given the possibility of heparin resistance in COVID-19, antiplatelet agents are being considered as potential alternatives. In a retrospective analysis of 192 consecutive COVID-19 patients admitted to 5 Italian hospitals, pre-admission treatment with anticoagulant (13.5%) or antiplatelet (28.6%) therapy was not protective from ARDS or death, although incidence of thrombosis was not reported [128]. An uncontrolled study in critical COVID-19 patients in Italy suggests that a combination of enhanced prophylactic dose heparin, clopidogrel loading and subsequent maintenance, and antithrombin correction returns viscoelastic tests to essentially normal [129]. A phase IIb trial in Italy treated 5 patients with severe respiratory failure due to COVID-19 with combination therapy of tirofiban, aspirin, clopidogrel, and fondaparinux [130]. They then selected controls matched for COVID-19 severity given either prophylactic or treatment-dose heparin, finding combination treatment superior in terms of improvement in oxygenation, and CPAP weaning time.

Initial advice suggested avoidance of aspirin and non-steroidal anti-inflammatory drugs in COVID-19 due to the possibility of intra-alveolar haemorrhage and DIC [131–133]. However, the detection of antiphospholipid antibodies in just under half of COVID-19 patients in one study [134] provides a hint for possible benefits of aspirin, a recognised treatment for antiphospholipid syndrome [135], in COVID-19. Studies of aspirin in COVID-19 are scant, however and whether the presence of antiphospholipid antibodies here represents a false positive as simply a reactive response to infection remains unclear [136]. At the time of writing, at least one trial of aspirin in COVID-19 is recruiting patients (NCT04365309), and a second has completed recruitment (NCT04368377).

In one of the few prospective studies involving anticoagulants in COVID-19, Liu et al. performed a multi-centre parallel randomised controlled trial of 31 patients with severe or critical COVID-19, 17 of whom were given standard of care, while 14 were given dipyridamole 50 mg three times daily for 14 days in addition to standard of care [137]. While no information about other anticoagulation was provided, the group reported an increased survival and remission rate in the dipyridamole group approaching statistical significance (odds ratio 23.75, $p = 0.06$), as well as reduced D-dimer levels, and increased lymphocyte and platelet counts. Their in silico docking studies and in vitro cell culture results published in the same paper reveal that dipyridamole appears to suppress viral replication. Three clinical trials are in progress at the time of writing (NCT04391179, NCT04424901, and NCT04410328), the results of which are eagerly awaited given the promising results of this initial study.

While currently there is insufficient evidence to recommend antiplatelet therapy in all patients suffering from critical COVID-19, initial results appear promising. Current guidelines maintain that antiplatelet therapy should be continued in patients with acute coronary syndrome [131] and acute stroke [26], although it should be noted that lopinavir/ritonavir may increase or decrease the activity of a multitude of the antiplatelet agents via hepatic enzyme inhibition [138].

6.4. Direct thrombin inhibitors

Some guidelines have recommended direct antithrombin inhibitors in patients with COVID-19, especially if heparin-induced thrombocytopenia is suspected [139], though few studies exist. Increased plasma concentration of dabigatran (along with the other direct-acting anticoagulants) has been observed in patients treated with lopinavir/ritonavir [140], raising the possibility of a class effect leading to unpredictable plasma levels in patients treated with antivirals. One study of severe COVID-19 patients at the Royal Brompton Hospital, UK, reports the successful use of argatroban titrated to APTT as an anticoagulant in patients resistant to heparin due to antithrombin deficiency, which renders heparin ineffective [141]. While 8 of 10 were on ECMO, 30% experienced bleeding. One interesting caution in treatment with direct thrombin inhibitors is a falsely low Clauss fibrinogen level due to interference of the exogenous thrombin component of the assay [142].

6.5. Nafamostat mesylate

The serine protease inhibitor nafamostat mesylate has been in use in Japan for many years as an anticoagulant specifically in DIC, with very few haemorrhagic side effects. It was identified as a potential target early in the pandemic due to its known inhibitory effect on MERS-CoV membrane fusion [143]; it has now been confirmed to inhibit SARS-CoV2 infection in vitro [144–146]. Combining nafamostat with heparin to supplement its anticoagulant effects, which are less prominent than its antifibrinolytic effects, has been suggested in COVID-19 [147]. An uncontrolled three patient case series from South Korea argues improvement with nafamostat treatment [148], however much further work is required. Two clinical trials have thus far been registered (NCT04418128 and NCT04352400).

7. Conclusion

COVID-19 clearly results in both systemic arterial and venous thrombi even in mild infection, as well as a likely localised pulmonary microthrombosis resulting in severe and possibly atypical ARDS. While reduced compliance is normally a hallmark of ARDS, the disproportionate hypoxia relative to preserved compliance observed in COVID-19 ARDS is theorised to be a result of shunting due to this pulmonary microthrombosis, highlighting the importance of further study of the coagulation system in this illness. While it is difficult to de-entangle the relationship between elevated D-dimer, mortality, and the comorbidities brought together in a COVID-19 patient, D-dimer level indeed appears to be prognostic, as do other markers of coagulation dysfunction such as thrombocytopenia. The development of an atypical pro-coagulant DIC is frequent among non-survivors, with a paucity of bleeding events. While VTE typically declares itself clinically, PE presents a challenge for diagnosis when co-presenting with COVID-19 due to the significant overlap in clinical picture, likely leading to its under-reporting. Difficulties in transport for imaging, as well as the oft-observed renal impairment make contrasted studies to visualise the pulmonary vascular tree problematic. While arterial occlusive events in the limbs or mesentery are often obvious clinically, subtle neurological features associated with cerebrovascular events may be missed due to sedation in ICU. Thus, high clinical suspicion, liberal investigation, and possibly screening of patients on ICU may be appropriate.

Treatment of COVID-19 hypercoagulability remains an area of ongoing debate and investigation. Heparin appears beneficial, although whether these effects are due to reduction in risk of VTE in already hypercoagulable patients, or are treating a separate COVID-19-induced disease process remains unclear. While ICU patients in the UK are routinely given prophylactic heparin, few studies compare this with higher doses of heparin. Failure of prophylactic-dose heparin, the observed lack of bleeding in COVID-19 patients, and the emerging possibility of heparin resistance has led clinicians in some centres to explore use of treatment-dose anticoagulation, even in the absence of traditional indications, on a case-by-case basis. There does appear to be a subgroup of severe COVID-19 patients who particularly benefit from heparin, but prospective identification of this group is difficult based on the current data. We feel that this is an important area for future research. Current ISTH guidelines recommend prophylactic doses of LMWH for all hospitalised COVID-19 patients, in the absence of contra-indications [149]. Thrombolytic agents provide a possible avenue for further exploration, although fear of haemorrhage has thus far confined their use to a last ditch attempt to salvage patients when mortality appears certain. Antiplatelet agents appear beneficial and comparatively free from side-effects, although further investigation is needed. To the authors' knowledge, the efficacy of warfarin and the direct-acting oral anticoagulants (with the exception of dabigatran) have not yet been studied in COVID-19. As for all the treatments above, published randomised controlled trials are currently lacking; thus hypercoagulability in patients with COVID-19 represents a potentially rich area for future research in reducing the morbidity and mortality of this novel illness.

Declaration of competing interest

The authors declare that they have no conflicts of interests.

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