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Understanding the andromeda strain – The role of cytokine release, coagulopathy and antithrombin III in SARS-CoV2 critical illness

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1. Introduction

As the novel coronavirus, SARS-CoV2, continues to spread across the globe and infect millions of people worldwide [1], we are only just beginning to understand and study this disease as it manifests. The panoply of presentations is best described in a recent systematic review of 31 articles including nearly 50,000 patients; 30% require ICU level care, 30% develop Acute Respiratory Distress Syndrome (ARDS) and 8% suffer Multi-Organ Dysfunction (MOD) [2]. Putative risk factors of critical illness and predictors of mortality have been extensively reported from China since the outbreak in December 2019. Older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer greater than 1 μg/ml (1000 ng/ml) on admission have been associated with increased odds of in-hospital death [3]. Comorbidities such as diabetes and cardiovascular disease, including hypertension, also contribute to the morbidity associated with this disease [4]. Presentations can vary and include pulmonary manifestations such as shortness of breath and hypoxemia, kidney dysfunction and oliguria, central nervous system (CNS) dysfunction with altered mental status, and laboratory derangements such as hyperbilirubinemia, acidosis, elevated lactic acid, coagulopathy, and thrombocytopenia [5].

Management of this illness also continues to be of much debate. A recent paper by Gattinoni et al challenges current European sepsis guidelines on the ventilatory management of patients with acute respiratory failure from COVID-19 by proposing a phenotype of lung injury that may not respond to traditional ARDS management. The phenotype, dubbed Type L, manifests with compliant and poorly recruitable lungs and hypoxemia out of proportion to imaging findings likely due to alterations in the ventilation perfusion (V/Q) ratio [6]. We propose that in situ thrombosis of the pulmonary vasculature along with a systemic thrombotic secondary to an underlying coagulopathy likely contributes to the V/Q mismatch given findings on autopsy showing clot burden within the blood vessels of open lung specimens [7–10]. Ventilation to areas with obstructed pulmonary vessels improve while adjacent normal areas of lung, that receive redistributed pulmonary blood flow, may be under-ventilated resulting in hypoxemia [11]. In addition, a systemic thrombosis may reduce perfusion to vital organs resulting in multi-organ failure. This is further supported by a recent study out of Wuhan, China which showed that 25% of 81 critically ill patients developed lower extremity venous thrombosis [12], while 35% of 184 ICU patients in Dutch hospitals with COVID-19 suffered pulmonary embolism [13]. Thrombotic sequelae of COVID-19 infections are clear and require

Keywords:
COVID-19
SARS-CoV2
SARS-CoV critical illness
Coagulopathy
Thrombosis
Heparin resistance
Antithrombin III

ABSTRACT

As the current coronavirus pandemic continues and cases of COVID-19 critical illness rise, physicians and scientists across the globe are working to understand and study its pathophysiology. Part of the pathology of this illness may result from its prothrombotic potential as witnessed from derangements in coagulation and thrombotic complications reported in observational studies performed in China and Europe to findings of micro-thrombosis upon autopsy analysis of patients who succumbed to COVID-19. Multiple organizations, including the American Society of Hematology (ASH), recommend the routine use of prophylactic heparin to temper the thrombotic complications of this illness given its mortality benefit in severe COVID-19 infections. Reductions in circulating levels of Antithrombin III (AT), the primary mediator of heparin resistance, as a prognostic marker, an important effector of heparin resistance, and a potential therapeutic target for COVID-19 remains to be explored.

ARTICLE INFO

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https://doi.org/10.1016/j.blre.2020.100731

Available online 3 July 2020
further study into both the inflammatory and thrombotic nature of this illness.

2. Cytokine storm, endothelialopathy and coagulopathy in COVID-19

Beyond hypoxemia and lung injury, SARS-CoV2’s pathogenicity likely involves an uncontrolled activation of the immune system. Critically-ill patients out of one hospital in Wuhan, China had higher levels of inflammatory cytokines including Interleukin-2 (IL2), IL7, IL10, Granulocyte-colony stimulating factor (G-CSF), Interferon gamma-induced protein 10 (IP10), and Tumor necrosis factor alpha (TNF α) [14]. The inflammatory elements of this disease are further supported by a retrospective analysis of 68 death cases from Jin Yin-tan Hospital and Tongji Hospital in Wuhan, China. Ruan et al suggested that predictors of mortality included elevated Interleukin-6 (IL-6) (11.4 pg/ml in non-

| Table 1 | Inflammatory and Hematological profile of patients with SARS-CoV2. |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Statistical Measure | Hgb(11.3–17) (g/ dl) | WBC (4–11) (10³)/ cmm | Lymphocyte count (1–4.8) (10³)/ cmm | Ferritin (11–336) 2 (ng/ml) | IL-6 (≤ 1–8) (pg/ml) |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Zhou et al [3] | | | | | |
| Survivors | Median | (12.0–14.0) | (4.3–7.7) | (0.8–1.5) | (503.2 ± 921.5) | (5.0–7.9) |
| (n = 137) | | | | | |
| Non-Survivors | Median | (12.6 ± 1.0) | (6.9–13.9) | (0.5–0.8) | (1435.3 ± 2000) | (7.5–14.4) |
| (n = 54) | | | | | |
| Cui et al [13] | | | | | |
| Non-VTE patients | Mean | 12.53 (±1.67) | 6.6 (±1.6) | 1.3 | |
| (n = 61) | | | | | |
| VTE patients | Mean | 12.32 (±1.65) | 7.8 (±1.3) | 0.8 | |
| (n = 20) | | | | | |
| Huang et al [14] | | | | | |
| No ICU care | Median | 13.05 (SD) | 5.7 (±1.0) | 1.0 | |
| (n = 28) | | | | | |
| ICU care | Median | 12.2 (±2.0) | 11.3 (±0.6) | 0.4 | |
| (n = 13) | | | | | |
| Ruan et al [15] | | | | | |
| Discharged Cases | Mean | 12.76 (SD) | 6.76 (±1.42) | 1.2 | 614 (±1030.9) |
| (n = 82) | | | | | |
| Death Cases | Mean | 12.7 (1.67) | 10.62 (4.76) | 0.6 | 1297.6 (±32) |
| (n = 68) | | | | | |
| Zhang et al [23] | | | | | |
| Patient 1 | N/A | 11.1 (SD) | 17.79 (±0.43) | 0.43 | |
| Patient 2 | N/A | 9.9 (SD) | 6.73 (±0.29) | 0.29 | |
| Patient 3 | N/A | 9.2 (SD) | 8.71 (±0.79) | 0.79 | |
| Guan et al [24] | | | | | |
| Non-severe patients | Median | 13.5 (IQR) | 4.9 (11–14.8) | 1.0 | |
| (n = 926) | | | | | |
| Severe patients | Median | 12.8 (IQR) | 3.7 (11–14.1) | 0.8 | |
| (n = 173) | | | | | |
| Wang et al [42] | | | | | |
| Non-ICU patients | Median | 4.8 (IQR) | 4.3 (3.5–4) | 0.9 | |
| (n = 102) | | | | | |
| ICU patients | Median | 6.6 (IQR) | 6.6 (3.6–9.8) | 0.8 | |
| (n = 36) | | | | | |
| Yang et al [37] | | | | | |
| COVID-19 patients | Mean | 4.56 (IQR) | 1.2 (2–4.8) | 0.68 | |
| (n = 149) | | | | | |
| Panigada et al [44] | | | | | |
| Observations | Mean | 1485 (SD) | 13.8 (3.5) | 1.5 | |
| (n = 11) | | | | | |
| Spiezia et al [45] | | | | | |
| Controls | Mean | 13.8 (IQR) | 12.1 (11–16) | 0.6 | |
| (n = 44) | | | | | |
| COVID-19 patients | Mean | 12.1 (IQR) | 11.6 (11–16) | 0.6 | |
| (n = 22) | | | | | |
| Ramucci et al [32] | | | | | |
| Patient Baseline | Mean | 218 (SD) | 218 (116–300) | | |
| (n = 16) | | | | | |
| Follow-up 7 days | Mean | N/A | N/A | | |

Hgb = Hemoglobin, WBC = White blood cell count, IL-6 = interleukin 6, VTE = venous thromboembolism, SD = standard deviation, IQR = interquartile Range, N/A = not available. 

\* p < 0.05, 
\*\* p < 0.01, 
\*\*\* p < 0.001.
survivors vs 6.8 pg/ml in survivors; p < 0.001) and serum ferritin (mean 1297.6 ng/ml in non-survivors vs 614.0 ng/ml in survivors; p < 0.001) [15]. Elevated inflammatory markers appear to negatively influence survivability in COVID-19 and is a feature of other severe coronavirus infections.

Since novel 2019 coronavirus shares 79% of its genetic material with the SARS-CoV1 [16], it is not surprising that the critical illness manifestations of both coronaviridae would be similar. MOD in SARS-CoV1 is mediated by ACE2 receptor interaction with SARS-CoV spike protein and is akin to what has been described for SARS-CoV2 [17]. This interaction results in infection of the alveolar epithelium and subsequent upregulation of proinflammatory cytokines, including IL2, IL7, and TNFα [18]. Some experts have suggested that COVID-19’s inflammatory profile resembles that of secondary hemophagocytic lymphohistiocytosis (sHLH) [19]. Others have proposed COVID-19’s severe clinical course to be secondary to sepsis [3]. Both diseases are a consequence of “cytokine storm”, a syndrome characterized by overwhelming systemic inflammatory hyperferritinemia, hemodynamic instability, MOD, and death [20]. Data collected from critically ill patients summarized in Table 2, show statistically significant differences in inflammatory markers such as IL-6 and ferritin along with the hallmark reduction in lymphocyte count, a feature that appears to be present both in current and previous SARS pandemic viruses.

Cytokines are known disrupters of normal hemostasis in humans [28], and are likely one of the major contributors to SARS-CoV2 thrombotic potential by promoting an imbalance in prothrombotic and intrinsic anticoagulant pathways such as the loss of tissue factor pathway inhibitor (TFPI) action, imbalance of the protein C & S system, down regulation of thrombomodulin expression on endothelial cells, and reduction in serum levels of antithrombin III (AT) [29]. This cytokine blitz has been linked to coagulopathy in sepsis by means of a process called immunothrombosis. A variety of thrombotic triggers released during this event, including cytokines themselves, activated platelets, complement and neutrophil extracellular traps, have all been proposed to play a role in this disease process [30]. An interesting and important analysis by Ranaucci et al highlighted this well; 16 COVID-19 patients with ARDS had IL-6 levels that correlated with markers of thrombosis and hypercoagulability [32].

The SARS-CoV family’s affinuty to ACE2 expression on alveoli and vascular endothelial cells may also promote further inflammation by endothelial dysfunction, microvascular thrombosis and end organ dysfunction [33]. Evidence of SARS-CoV2 viral inclusion bodies in the endothelial cells resulting in endothelialitis and injury to lung, heart, kidney and liver have been reported in autopsy specimens of patients with COVID-19 [21]. Endothelial damage, exacerbated by underlying diabetes and hypertension, is another key determinant of thrombosis [22], which may explain why patients with cardiovascular risk factors do poorly with COVID-19 [34]. Endothelial activation, dysfunction and death result in the expression of prothrombotic factors such as P-selectin, von Willebrand factor and fibrinogen. Damaged endothelial feedbacks with activated platelets resulting in endothelial tissue factor expression, a potent activator of the clotting cascade [35]. The net effect of SARS-CoV2-related endothelial damage, cytokine-induced hypercoagulability and alterations in laminar blood flow induced by this sepsis-like syndrome may be the main factors resulting in the significant thrombotic morbidity seen with COVID-19 but other mechanisms have also been proposed.

SARS-CoV2’s virus for the ACE receptor has also been connected to glomerular disease given findings of nephritic disease in postmortem kidney samples from patients with COVID-19 [36]. It is possible that that a nephrosis resulting in the loss of endogenous anticoagulants may be another cause of a dysregulation in the coagulation system and Gross et al recommend serial urinalysis to monitor for this complication [36]. Finally, recent evidence derived from the serologic analysis of three patients with digital ischemia and cerebral infarcts admitted to the ICU in Wuhan’s Tongji Hospital have also shown positivity for antiphospholipid antibodies, which may be byproducts of viral infection or a mediator of thrombosis [23]. Its significance however remains to be explored.

3. Hemostatic abnormalities and the SARS family of viruses

The concern for coagulopathy in COVID-19 initially had arisen from the strikingly elevated levels of fibrin degradation products and D-dimer measurements, first reported by Guan et al [24]. Since then, alterations in hemostasis have been published in patients with critical illness secondary to COVID-19 and are summarized in Table 2. Marked elevations in D-Dimer are apparent in patients who have ARDS [39], are non-survivors [5,40], suffer from critical illness [14,24,41,42], and develop deep vein thrombosis [12]. Thrombocytopenia is present though appears mild and is typically not less than 100 × 10^3/cmm (see Table 2). Thus far, two studies have described significant prolongation of prothrombin time (PT) and activated partial thromboplastin time (PTT) in patients with COVID-19 [12,40].

This combination of abnormalities is indicative of a coagulopathy reminiscent of disseminated intravascular coagulation (DIC) but phenotypically different from DIC associated with other inflammatory syndromes like HLH, marked by significant hypofibrinogenemia [25], and sepsis, marked by significant thrombocytopenia [26]; major abnormalities in fibrinogen and platelet count have not been recorded in severe or critically ill SARS-CoV2 patients (see Table 2). In addition, though mimicking DIC, COVID-19 coagulopathy does not fit criteria for overt DIC set by the International Society of Thrombosis and Hemostasis (ISTH) [27]. So far only one study has demonstrated a trend to overt DIC after Day 7 of admission in 71 4% of survivors vs 0.6% of non survivors [40]. Clinical evidence of DIC manifesting with ecchymosis of the fingers and toes in conjunction with worsening cardiac and renal dysfunction has also been reported in COVID-19 patients requiring intensive care with a positive DIC profile [43]. DIC is distinguished by the occurrence of systemic or widespread vascular thrombosis resulting in inadequate blood supply to various organs and MOD [27]. DIC is a common but fatal consequence of cytokine storm and is a significant predictor for MOD and mortality [26] but is likely not the major driving force for coagulopathy and critical illness seen in COVID-19. Finally, hypercoagulability has also been described using Thromboelastography with three studies to date describing decreased reaction time (R) or clotting time [44,45] and K value or maximum clot firmness [32,44,45]. This constellation of abnormal coagulation parameters suggest a coagulopathy likely associated with profound inflammation mediates the thrombotic complications of SARS-CoV2.

Thrombotic events secondary to severe pulmonary insults may not be unique to COVID-19 and can be contrasted to other similarly devastating diseases. Coagulopathy is a rare manifestation in SARS-CoV1 [46,47], the virus responsible for the 2003 SARS epidemic, with fewer than ten patients out of 239 cases reviewed by Leong et al resulting in DIC and thrombocytopenia [46]. These reductions in platelet count have been found to correlate well with mortality [38,48] and may be responsible for findings of pulmonary hemorrhage in SARS-CoV1 autopsies [49]. Evidence of DIC manifesting with elevated D-dimer, prolonged PT, and microthrombosis within alveoli capillaries and thromboembolic bronchial arterioles have also been described in other autopsy specimens of SARS-CoV1 patients [50]. Recent evidence contrasting the coagulation features between severe pneumonia induced by COVID-19 and other causes of pneumonia show a significantly higher platelet count among those with SARS-CoV2 but relatively similar levels of D-Dimer and PT prolongation [51]. Interestingly, a prospective study from France show a higher odds of thromboembolic outcomes in COVID-19 ARDS patients when compared with non-COVID-19 ARDS patients after propensity score matching (OR 2.6 [1.1–6.1], p = .04) [39].
| Table 2   | Coagulation profile of patients with SARS-CoV2. |
|-----------|-----------------------------------------------|
|           | Statistical Measure | D-dimer (0–240) | AT (78–126) | PT (12–14.5) | aPTT (25–35) | Platelets (150–400) | FIB (220–498) | FDPs (<10) |
| Zhou et al [3]                  | Survivors (n = 137) | 600             | 11.4        | 220         |
|                                   | (IQR)               | (300–1000)      | (10.4–12.6) | (168–271)   |
| Non-Survivors (n = 54)          | Median (IQR)        | 5200            | 12.1        | 165.2       |
|                                   | (1500–21,100)       | (11.2–13.7)     | (107–229)   |
| Cui et al [12]                  | Non-VTE patients    | Mean 800        | 15.6        | 248.8       |
|                                   | (±SD)               | (±1200)         | (±1.0)      | (±4.5)      |
|                                   | (n = 61)            | (±3000)         | (±1.0)      | (±6.4)      |
|                                   | (n = 20)            | (±1117)         |             | (±1106)     |
|                                   | VTE patients        | Mean 5200       | 15.4        | 246.6       |
|                                   | (n = 28)            | (9.8–12.1)      | (36.9–44)   |
|                                   | ICU care (n = 13)   | Median 2400     | 12.2        | 196         |
|                                   | (IQR)               | (700–14,400)    | (22.5–33.9) |
|                                   | COVID-19 (n = 162)  | Median 610      | 10.7        | 149         |
|                                   | (IQR)               | (350–1290)      | (36–94)     |
|                                   | Non-Survivors       | Median 2120     | 15.5        | 516         |
|                                   | (n = 21)            | (84)            | 44.8        |
|                                   | (IQR)               | (770–5270)      | (40–2.51)   |
|                                   | COVID-19 Patients   | Discharged Mean | 222.1       |
|                                   | (n = 82)            | (SD)            | (78)        |
|                                   | Death Cases Mean    | 173.6          |
|                                   | (n = 68)            | (SD)            | (67.7)      |
| Han et al [41]                   | COVID-19 Patients   | Control group Mean | 260        |
|                                   | (n = 40)            | (±SD)           | (98.82)     |
|                                   | SARS-CoV-2 patients | (±12.91)        | (12.08)     |
|                                   | (n = 150)           | (±5.28)         | (28.65)     |
|                                   | (IQR)               | (±3.03)         | (29.01)     |
|                                   | COVID-19 Patients   | Non-ICU patients Mean | 166       |
|                                   | (n = 102)           | (IQR)           | 12.9        |
|                                   | ICU patients        | Median 414      | 13.2        |
|                                   | (n = 36)            | (IQR)           | 30.4        |
|                                   | COVID-19 Patients   | Mean; Median 220| 12.20       |
|                                   | (n = 149)           | (±SD); (IQR)    | 33.29       |
|                                   | Observations Mean   | 4877            | 1.16        | 348         |

(continued on next page)
In a prospective study of 449 patients with severe COVID-19, nearly 100 coagulopathy that have supported the use of heparin in this population. ASH has also put forth Food and Drug Administration (FDA) approved Direct Oral Anticoagulants (rivaroxaban, betrixaban) after discharge in daily for at least 31 days or betrixaban 160 mg load on day 1 followed by [54] and the American College of Cardiology [55] echo these findings; thrombophilia, severe immobility and an elevated D-dimer. [53] Other ISTH recommend extended duration of thromboprophylaxis ranging risk of heparin-induced thrombocytopenia [53]. Updated guidelines ular weight heparin (LMWH). Those with major organizations such as the American Society of Hematology (ASH) recommended for comorbid obesity, severe thrombocytopenia or poor renal –4. The benefits and limitations of heparin

Currently, in addition to adequately treating the underlying cause, the International Society on Thrombosis and Hemostasis (ISTH) recommend that thrombotic complications of COVID 19 should be managed with the systemic administration of prophylactic doses of low molecular weight heparin (LMWH) in all hospitalized patients and not only the critically ill [52]. LMWH is preferred over unfractionated heparin given its less frequent, once daily, dosing schedule and lower risk of heparin-induced thrombocytopenia [53]. Updated guidelines now include the role of intermediate-dose LMWH (enoxaparin, 40–60 mg daily) for sicker patients with dose alterations also recom mend for comorbid obesity, severe thrombocytopenia or poor renal function [53]. In addition, in the absence of COVID-19 specific data, the ISTH recommend extended duration of thromboprophylaxis ranging from 2 to 6 weeks with LMWH (enoxaparin, dalteparin, tinzaparin) or Direct Oral Anticoagulants (rivaroxaban, betrixaban) after discharge in select individuals with low bleeding risk but with high VTE risk factors such as old age, ICU admission, malignancy, a previous history of VTE, thrombophilia, severe immobility and an elevated D-dimer. [53] Other major organizations such as the American Society of Hematology (ASH) [54] and the American College of Cardiology [55] echo these findings; ASH has also put forth Food and Drug Administration (FDA) approved regimens for post discharge prophylaxis including rivaroxaban 10 mg daily for at least 31 days or betrixaban 160 mg load on day 1 followed by 80 mg daily for at least 35 days [54].

These guidelines stem from studies specific to COVID-19 induced coagulopathy that have supported the use of heparin in this population. In a prospective study of 449 patients with severe COVID-19, nearly 100 patients met ISTH diagnostic criteria for sepsis-induced coagulopathy (SIC) and received either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Those with SIC diagnostic criteria (≥4) and markedly elevated D-Dimer exceeding 3.0 μg/ml had lower rates of 28-day mortality when treated with prophylactic heparin compared to heparin non-users (40-0% vs 64-2%, P = 0.029 and 32-8% vs 52-4%, P = 0.017 respectively) [56]. Another study by Yin et al showed that patients with COVID-19 also achieve 28-day mortality benefit from prophylactic heparin when D-dimer levels >3-0 μg/ml (six-fold of upper limit of normal, 6xULN) compared to heparin non-users (32-8% vs. 52-4%, P = 0.017) which was significantly different when compared to patients with pneumonia secondary to causes other than COVID-19 [51]. Therapeutic anticoagulation is also under investigation. Observational analysis of nearly 400 critically ill hospitalizations in Mount Sinai Hospital in New York showed reduced in-hospital mortality among those who were mechanically ventilated and treated with full dose anticoagulation when compared to those who were not therapeutically anticoagulated (29.1%, median survival of 21 days vs 62.7%, median survival of 9 days) [57]. Beyond its anticoagulant effect, however, heparin has been shown to be anti-inflammatory [58]. Interleukin 6 (IL-6) is a known pro-coagulant [28] and pro-inflammatory agent released as part of the cytokine storm seen in severe cases of COVID-19 [59]. Some have proposed that heparin could attenuate this SARS-CoV2 cytokine storm [60] but further studies are needed to support this notion and trials are ongoing [31]. Thus far, the consensus supports the role of intermediate-dose anticoagulation for those admitted to the ICU, especially those with ARDS, while restricting full dose anticoagulation to those with confirmed VTE and presumed PTE [30].

Reasons for heparin’s success continues to be hotly debated across the globe. The use of heparin prophylaxis in a critical care setting is considered routine practice in the United States and most European countries but is not standard of care worldwide among hospitalized patients [61]. Large observational studies out of China analyzing the prevalence of routine venous thromboembolism (VTE) prophylaxis in COVID-19 patients show poor use of anticoagulation at a rate much lower than the those considered high risk for VTE by Padua prediction scores [62]. Critical illness and ICU stay are known risk factors for VTE [63] and are frequent requirements for COVID-19 infection as discussed above. While this disparity in routine VTE prophylaxis use in critically ill COVID-19 patients may explain why thrombosis is a commonly reported phenomenon from the East, European nations, such as the Netherlands and France, have reported ongoing VTE issues despite adherence to

| Measure         | D-dimer (0–240) | AT (78–126) | PT (12–14.5) | aPTT (25–35) | Platelets (150–400) | FIB (220–498) | FDPs (≤10) |
|-----------------|----------------|-------------|--------------|--------------|---------------------|--------------|------------|
| Stat. (n = 30)  | (Min–Max)      | (ng/ml)     | (%)          | (s)          | (10^3/mm)           | (mg/dL)      | (mg/L)     |
| (n = 44)        | (±SD)          |             | (±14)        | (±2)         | (±67)               | (±78)        |            |
| COVID-19 Patients | (±SD)          | 225         | 90           | 26           | 218                 | 297          |            |
| Ranucci et al [52] | (±SD)          | 2099        | 13           | 12           | 119                 | 148          |            |
| (n = 16)        | (IQR)          | 3500        | 85           | 36-4         | 271                 | 794          |            |
| 7 days          | (IQR)          | 2500        | 107          | 44           | 320                 | 582          |            |
| (n = 449)       | (±SD)          | 2600-2800   | 81–130       | 42-1-47-4    | 308–393             | 446-621      |            |
| Yin et al [51]  | (n = 104)      | 2920        | 152          | 215          |                     |              |            |
| (n = 449)       | (±SD)          |             | (±5)         | (±5)         | (±100)              |              |            |
| Non-COVID PNA   | Mean; Median   | 2520        | 16-2         | 188          |                     |              |            |
| (n = 449)       | (±SD; IQR)     | 1400-5810   | (±5)         | (±98)        |                     |              |            |
| COVID PNA       | Mean; Median   | 1940        | 15.2         | 215          |                     |              |            |
| (n = 449)       | (±SD; IQR)     | 900-9440    | (±5)         | (±100)       |                     |              |            |

AT = Antithrombin, PT = Prothrombin Time, aPTT = Activated partial thromboplastin time, FIB = fibrinogen, FDPs = Fibrin degradation products, PNA = Pneumonia, VTE = venous thromboembolism, SD = standard deviation, IQR = interquartile Range, N/A = not available, no. = number.

a p ≤ 0.05
b p ≤ 0.01
c p ≤ 0.001.

| AT observations: n = 11; APTT ratio: reference range = 0.7–1.2. PT (%): reference range ≥70%. PT ratio: reference range = 0.84–1.20. |
prophylaxis protocols [39,64]. Klok et al reported a cumulative incidence of confirmed diagnoses of PE, deep-vein thrombosis (DVT), ischemic stroke, myocardial infarction or systemic arterial embolism of 57% (95% CI 47–67%) in 184 ICU patients with COVID-19 from 3 Dutch hospitals [13] with 27% (95% CI 17–37%) possessing CT angiography and/or ultrasonography confirmed VTE despite routine use of nandoparin prophylaxis per local protocol on an earlier analysis of the same cohort [64]. In a French prospective study of 2 tertiary hospitals, a high prevalence of thrombosis (27%), largely pulmonary embolisms (16.7%), occurred despite baseline heparin treatment [39].

At this time, both microvascular and macrovascular events appear to be a consequence of coronavirus associated coagulopathy; supportive care and heparin remain the only recommended therapeutic options [30]. Although a conservative approach may be beneficial, there remains a paucity of data surrounding the use other therapeutic options or adjuncts outside of what is considered best practice. Experts have proposed that the mechanism of localized thrombosis in SARS-CoV2 infected patients may differ from those usually described in ICU patients [39]. We propose that further study into the role of heparin's primary effector, Antithrombin III (AT), may help explain some of the difficulty witnessed with the antithrombotic management of this illness.

5. The potential role of Antithrombin III

5.1. Antithrombin III deficiency and COVID-19

AT is a plasma glycoprotein made in the liver and its role is to block the action of coagulation enzymes such as thrombin, plasmin, and factors IXa, Xa, XIa, XIIa [65]. AT levels in normal human plasma range from 2.57 μM, or 0.125 mg/ml to 0.160 mg/ml which is associated with 80%–120% activity [66]. Hereditary reductions in AT activity may reach levels of 40–60% while acquired reductions, as seen in severe sepsis, may reduce AT activity to as low as 30% [67]. There is no current consensus to what AT level is defined as deficient but an AT level of at least 70% is necessary for effective inhibition of the coagulation cascade [68]. Nevertheless, mild AT deficiency has been associated with increased odds of developing VTE in a dose-response fashion (86–100% vs >100%, OR 1.31 [1.11–1.54]; 76–85%, OR 2.00 [1.44–2.78] and 61–75%, 4.77 [1.93–11.83]). Similar subnormal reductions in AT have been described in COVID-19 related illness and summarized (see Table 2). In the paper by Han et al, patients with SARS CoV2, were noted to have significant reductions in AT levels nearing 80% with the lowest quartile of patients with critical illness suffering levels close to 66% (n = 10, AT:% 82.44 ± 15.89) [41]. Tang et al showed statistically significant reductions in AT after day 7 of admission in nonsurvivors with the lowest quartile levels as low as 75% vs 85% in survivors (p < .05) [40]. Panigada et al reported that a randomly selected group of 24 ICU patients with COVID-19 had TEG parameters consistent with a hypercoagulable state with 11 patients having a mean AT activity of 74 (45–120%) and 55% of patients possessed less than the lower limit of normal AT activity (lower limit of normal = 82%) [44]. Ramucci et al reported mean AT activity of sixteen patients with COVID-19 to be 85% [65–91%] with 25% of patients with AT activity <80% [32]. Investigators at the University Medical Center Goettingen (UMG) in Germany detected even lower antithrombin III concentrations ranging from 26 to 62% [normal AT >70%] [36]. We speculate that understanding how AT activity varies with SARS-CoV2 critical illness may help bridge the gap between mortality and survivability but how COVID-19 results in reductions of AT remains a mystery.

Acquired AT deficiency is most commonly due to liver dysfunction [69], DIC [69], plasma losses by inflammatory conditions that increase vascular permeability [70], or loss in urine as a consequence of nephrotic syndrome [71]. Although liver dysfunction has not been reported with COVID-19, we speculate that low AT levels in critical illness induced by SARS-CoV2 is likely due to some combination of the above insults, cytokine-related impairment in endogenous anticoagulant levels [72] and consumption during coagulopathy (see Fig. 1). Renal losses are especially interesting given proteinuria is seen in nearly 44% of patients admitted to hospitals in Wuhan, China and nearly 10% of patients had near nephrotic range disease [73]. Centers in Germany have also recorded low AT levels, severe hypoalbuminemia and urine samples positive for blood, albumin, and leukocytes concerning for a possible nephritic component to COVID-19 infection [36]. AT plays an essential role in regulating coagulopathies such as DIC [74] and anticoagulants like heparin [75]; we believe AT may offer potential uses such as: a marker of mortality, heparin resistance, and therapeutic intervention in coronavirus associated coagulopathy.

5.2. Antithrombin III as a marker of disease severity

The correlation between AT reduction to clinical outcomes can be extrapolated from studies in sepsis where this association has already been well established [76]. In one series analyzing hemostatic abnormalities in sepsis, AT levels were significantly lower on days 1, 4, and 7 of severe sepsis nonsurvivors (peak activity of 75%) compared to survivors who displayed a trend to normalization on days 4 and days 7 from presentation [77]. In another series of 60 patients with septic shock, initial AT levels had the best prognostic value for prediction of mortality as compared with other antithrombotic markers including protein C and S [78]. Studies to date have only compared AT levels on admission but data on serial measurements to monitor for decline are lacking (see Table 2). To date, only Tang et al have reported how statistically significant reductions in AT occur in nonsurvivors of COVID-19 patients compared to survivors after day 7 of admission and this reduction seems to persist even until day 14. A trend to DIC after Day 7 is witnessed in nonsurvivors where statistically significant increases in PT, PTT and D-Dimer levels occur while Fibrinogen levels significantly drop [40]. D-dimers, a sensitive marker of thrombosis, may also be elevated in other conditions including cancer, surgery, connective tissue disease, lung disease, and pregnancy and this may result in false positive values for thrombosis [79]. More specific markers of thrombin formation and antithrombin consumption include Thrombin-antithrombin complexes (TAT) [80]; TAT may also be a signal to the immunothrombosis of the sepsis syndrome and correspond to severity of sepsis and tissue hypoxia [80]. and recent work by Jin et al have shown that TAT correlates with disease severity in COVID-19 and differs significantly from levels reported in non-survivors (p < .05) [81]. D-dimer, however, appears to be a widely-accepted predictor of poor survival in SARS-CoV2 and more studies are needed to understand how AT levels on admission and serial measurements influence COVID-19 related coagulopathy and death.

5.3. The potential benefit of AT concentrate

In addition to its predictive power and anticoagulant properties, AT further displays anti-inflammatory properties when delivered as AT concentrate (ATc). AT exerts its anti-inflammatory action indirectly by inhibiting proinflammatory coagulation enzymes, directly by inducing endothelial prostacyclin synthesis, and further by interfering with leukocyte migration and adhesion to endothelial cells [67]. Currently, the ISTH claim the use of AT to treat COVID-19 to be experimental [52]. A recent review in the Journal of the American College of Cardiology have asked for more investigations to be performed using AT concentrates in moderate to severe COVID-19 infections or confirmed DIC [53]. Ramucci et al showed that antithrombotic support with therapeutic doses of LMWH, AT concentrate to corrected values <70% and clopidogrel load for platelet count >400,000 cells/μl in 16 COVID-19 pneumonia or ARDS patients with a pro-coagulant TEG resulted in statistically significant reductions in clot strength, fibrinogen levels, D-dimers and a normalization of TEG parameters in survivors of this illness. The authors proposed that this regimen may have thwarted a trend to DIC mentioned previously [32]. No studies to date have described how ATc may result in mortality benefit in COVID-19 critical illness. We believe AT to be a...
therapeutic agent worth exploring to temper the cytokine storm and coagulopathy associated with SARS-CoV2 as witnessed by ATc’s positive findings in many sepsis-related clinical trials.

Earlier trials looking at AT supplementation in severe sepsis and baseline AT levels close to 50% in patients who received intravenous loading dose of 3000 IU AT III followed by a maintenance dose of 1500 IU every 12 h for 5 days achieved a 39% reduction in 30-day all-cause mortality, improved organ failure scores, and better resolution of pre-existing organ failures [82]. Others have shown survival benefit in septic shock and AT activity <70% using 24,000 units of ATc over 5 days [83]. The largest and most recent prospective trial to date using ATc in sepsis is the double-blinded, placebo-controlled, multicenter phase 3 clinical trial conducted by Warren et al named the KyberSept trial [84]. Over 2000 adults were randomized into 2 equal groups both with baseline AT <60% receiving either intravenous antithrombin III (30,000 IU in total over 4 days) or placebo. Although intravenous AT had no impact on 28-day all-cause mortality, the results from this large study must be interpreted with caution given that AT was supplemented irrespective of whether DIC was present or not. An interesting and important subanalysis derived from this trial of 229 patients with DIC and low baseline AT <60% showed a significantly lower 28-day mortality rate (25% vs 40%; p = 0.02) in those who received ATc without adjuvant heparin (n = 114) vs. matched controls (n = 115) [85]. Additionally, a similar but larger multicenter retrospective controlled study of over 9000 patients with severe pneumonia and sepsis-related DIC found that AT administration was associated with a 9-9% (95% CI 3.5–16-3) reduction in 28-day mortality and reduced ventilation periods [20-6 vs 17.9 days; p = 0.001] in contrast to patients that did not receive AT [86]. There is no consensus on the correct dose, frequency and duration of AT supplementation at this time.

5.4. AT and heparin resistance in COVID-19

Although heparin is the only recommended agent to manage the thrombotic issues of sepsis-induced DIC [27], and currently for COVID-19, heparin resistance is a potential risk as it requires the presence of adequate AT activity to work effectively [75]. Ongoing thrombotic complications despite appropriate prophylaxis, as reported by French and Dutch COVID-19 cohorts, are concerning [39,64] and warrant further study as to why heparin may be failing and whether heparin resistance is playing a role. Although AT activity levels ≤60% are associated with a higher risk of developing heparin resistance [87], even subnormal levels between 60 and 70% have been associated with this phenomenon as well [88]. This concern is also present when considering options for anticoagulation in those undergoing continuous renal replacement therapy.

In a study of 78 patients with acquired AT deficiency (<70%) and septic shock requiring continuous renal replacement therapy (CRRT), anticoagulation with unfractionated heparin plus ATc supplementation prevented premature filter clotting [89]. Filter clotting with CRRT related to COVID-19 critical illness has been reported in nearly 97% of ICU patients in France with a median lifespan reported of an CRRT circuit as 1.5 [1.0–2.0] days compared to 3 days mentioned by the manufacturer with a third of patients having abnormal AT activity at baseline [39] and some centers are reportedly using bivalirudin instead while on CRRT [90]. Furthermore, heparin resistance may not be overcome solely by using additional doses as a randomized trial in patients with AT deficiency [56 ± 25% activity] requiring cardiopulmonary bypass showed more efficacy with treating the deficiency with AT concentrate alone rather than using escalating doses of heparin [91]. Other studies in the field of trauma, a disease which impacts coagulation similarly to sepsis and likely COVID-19, support this notion. In a study of 81 trauma patients, the incidence of DVT was thought to be related to the high prevalence of AT deficiency (67% of patients with AT ≤80%), and no difference was observed in DVT incidence with standard or higher doses of enoxaparin prophylaxis [92].

Finally, the incidence of thrombosis and renal injury requiring continuous renal replacement therapy (CRRT) is likely higher than previously thought as more data accumulates in this new disease, and little is known about how prophylactic doses of heparin impact the overall thrombotic morbidity relative to the reduced or subnormal AT levels witnessed in this population (see Table 2). Possible ways to circumvent this would be to examine Anti-factor Xa (Anti-Xa) levels to assess the efficacy of prophylactic heparin; a range of 0–2–0.5 IU/ml has been proposed [93]. Although there is a general concern for inadequate treatment with standard doses of prophylactic heparin in critically ill patients, the role of monitoring Anti-Xa is not well defined [93]. With these questions in mind, we must re-examine the routine use of heparin at prophylactic doses in COVID-19 patients as it pertains to thrombotic prophylaxis and CRRT as it may not be sufficient. Given the prevalence of clotting events despite heparin and issues surrounding AT activity in severe COVID-19 illness, we believe further studies into the right dose of

Fig. 1. Visual depiction of potential mechanisms by which SARS CoV2 infection results in reduction of circulating levels Anthrombin III and elicits end-organ damage.
heparin, the use of heparin alternatives like bivalirudin and the concurrent optimization of AT activity with ATc should be explored as possible avenues to thwart the thrombotic morbidity associated with this illness. ATc supplementation may hold the answer to manage COVID-19 patients with acquired AT deficiency, heparin resistance, elevated coagulopathy markers, and multiorgan dysfunction.

5.5. Limitations and risks associated with antithrombin III

Despite showing initial promise in sepsis-induced DIC trials, AT is not currently recommended in recently published "Surviving Sepsis Guidelines" in stark contrast to Japanese guidelines for septic DIC patients with AT activity <70% [94]. This is likely due to a meta-analysis of 11 RCTs studying endogenous anticoagulants in sepsis, 7 of which used AT, published by Freeman et al that showed no effect on mortality [95]. A subsequent larger cochrane meta-analysis assessing the benefits and harms of ATc in critical illness performed by Allingstrup et al showed no statistically significant effect of AT III on mortality with a relative risk (RR) of 0.95 [95% CI 0.88–1.03] for 30 RCTs. In addition, for those with severe sepsis and DIC, the RR for mortality was non-significant as well (0.95[0.88 to 1.03]). [96] An increased propensity for bleeding events (RR 1.58 [1.35 to 1.84]) was also noted when AT was compared to control; this was a secondary outcome derived from 11 RCTs. Nonetheless, the concomitant use of heparin with AT supplementation, the high risk of bias described in a majority of the RCTs and the heterogeneity of the populations included in the metaanalysis prevented any firm conclusions from being drawn. We agree with the Allingstrup and colleagues’ recommendations that more trials are needed to address the effect of AT alone in patients who suffer from critical illness and those who suffer from severe coronavirus related infections. Other risks of ATc supplementation include those intrinsic to the transfusion of any human derived blood product and include allergy, anaphylaxis and the transmission of infectious contaminants; no recent cases have been reported thus far [68]. Finally, this contagion has placed significant strain on blood banks as has been witnessed in China [97]. Thrombate III, a form of pooled AT derived from human serum, requires an intact supply chain and restrictive transfusion practices, indiscriminant use of blood products like AT may result in critical shortages for those with congenital AT deficiency who may suffer life-threatening perioperative and peripartum thromboembolic events [68].

6. Looking to the future

To date only Ranucci et al has described the potential role of AT supplementation in addition to therapeutic anticoagulation and antiplatelet loading but no firm conclusions could be made given its small sample size [32]. In a critical review of the hematologic complications of COVID-19 by Trepos et al, ATc supplementation for activity ≤50% has been proposed to treat COVID-19 patients who develop a non-overt DIC pattern of coagulopathy, as determined by the ISTH DIC score, assuming clotting factor II and V levels are >30% [98]. The relevant promise of ATc administration in sepsis and sepsis-induced coagulopathy and the shared inflammatory mechanism by which both sepsis and COVID-19 act, are one of many reasons for further trials to study the efficacy of ATc in the management of severe COVID-19 to address the underlying coagulopathy responsible for both the microvascular and macrovascular events described above. No firm recommendations regarding the right dose, route or minimum threshold for AT activity can be made for severe coronavirus related infections given the lack of trials in this field. A reasonable clinical trial framework would be to study those patients with significantly elevated D-dimers and/or elevated SIC scores and randomizing patients to either goal-directed ATc supplementation (activity levels >70%) with routine thromboprophylaxis or to standard of care; outcomes of interest would include the incidence of major thrombotic events, time to resolution of coagulopathy scores, length of stay in the ICU and mortality.

The complex interplay between SARS-CoV2 and its associated thrombotic phenotype is likely mediated by a cytokine storm that propagates a prothrombotic coagulopathy; one mechanism of interest is the reduction of serum levels of physiologic anticoagulants like Antithrombin III to subnormal degrees. This is supported by derangements in laboratory-derived coagulation profiles, the rising incidence of VTE events despite appropriate heparin prophylaxis, and the findings of microthrombosis on COVID-19 autopsy specimens described above. Although heparin will likely remain the mainstay to manage those with severe COVID-19 infection and a prothrombotic profile, further investigations are needed to help elucidate how other parameters of coagulation, such as AT, contribute to heparin resistance and the thrombotic morbidity of COVID-19. Also, properly performed trials are necessary to assess the efficacy of other agents like Antithrombin III concentrate in severe SARS-CoV2 infection.

6.1. Practice points

- SARS CoV2 is associated with a coagulopathy that may be secondary to the profound immune response its infection elicits from the body
- Heparin is the current standard of care for this complication though its efficacy appears to be limited and the evidence for it is sparse
- Antithrombin III deficiency, either to low or subnormal levels of activity, is witnessed in some cases of severe COVID-19 infection though its significance in COVID-19 coagulopathy pathogenesis and management remains to be elucidated

6.2. Research agenda

- Development of a registry of SARS-CoV2 patients with low or subnormal levels of Antithrombin III upon diagnosis and an intentional approach to the analysis of their long-term outcomes is necessary
- Measurement of Antithrombin III levels at the time of infection, throughout the disease course of coagulopathic patients treated with prophylactic heparin and upon changes in clinical status secondary to thrombosis are needed to help define AT’s role as a marker of prognosis, disease severity and an effector of heparin resistance
- Randomized, placebo-controlled trials regarding the right dose of anticoagulation, the empiric or goal-targeted supplementation of AT or the use of anticoagulation that operates independently of AT in COVID-19 critical illness are warranted

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgments

None.

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