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

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Exploring possible mechanisms for COVID-19 induced thrombocytopenia: Unanswered questions

Dear Drs Lillicrap and Morrissey,

We read with enthusiasm the recent article by Tang et al entitled "Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia," which is a retrospective analysis of the coagulation profile of 183 patients admitted with pneumonia secondary to the 2019-nCoV (COVID-19).[1] This article deals with a timely topic and brings up important points that need to be interrogated in future studies.

Tang et al reported 11.5% mortality in patients with COVID-19 pneumonia and noted that 71.4% of these deaths had abnormal coagulation profiles consistent with disseminated intravascular coagulation (DIC) based on criteria from the International Society on Thrombosis and Haemostasis (ISTH).[1] Compared to survivors of COVID-19 pneumonia, the non-survivors had significantly higher D-dimer and fibrin degradation product levels, and longer prothrombin time and activated partial thromboplastin time.[1] Consistent with the findings of Tang et al, a meta-analysis of 1779 patients with COVID-19 found that a low platelet count was associated with an over five-fold increased risk of severe disease (odds ratio [OR], 5.1; 95% confidence interval [CI], 1.8-14.6) and an even lower platelet count was associated with mortality in those patients.[2]

It is interesting that 57.1% of the non-survivors in the study by Tang et al (12 out of 21) exhibited thrombocytopenia (7 [33.3%] had 50 ~ 100 × 10^9/L and 5 [23.8%] had <50 × 10^9/L platelets).[1] While thrombocytopenia is a key diagnostic component in DIC, the data in this study raises a question of whether thrombocytopenia in COVID-19 is a part of sepsis-induced DIC and/or a direct platelet-viral interaction and if so, whether this interaction is beneficial for the host or for the virus and what the possible mechanisms are. These questions are worth exploring further in research studies.

The pathophysiology of DIC is complex, involving combined activation of the vascular endothelium, platelets, and leukocytes, and results in thrombin generation and widespread fibrin deposition.[3] There is multiple evidence that platelets interact directly with viral pathogens via pathogen recognition receptors (PRRs) and this is part of their role in fighting infections.[4] Platelets express PRRs such as C-type lectin receptors and toll-like receptors TLR-3, -7, and -9, which are reported to have a role in platelet-viral infections.[4] This interaction subsequently leads to platelet activation and release of molecules with antiviral activity including kinocidins and other microbicidal peptides.[4] Activated platelets are known to produce reactive oxygen species and can also interact with and activate other immune cells such as leukocytes, which can also fight and clear viral pathogens.[4] Activated platelets are cleared from the circulation by the reticuloendothelial system.[4,5] Thrombocytopenia has been reported with several viral infections such as human immunodeficiency virus (HIV), influenza, hepatitis B and C viruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and rhinovirus.[5]

Viruses can directly interact with platelets, thereby altering their count and/or function.[5,6]

Platelet-specific receptors known to interact with viruses are reported.[6] Various mechanisms were explained and are dependent on the virus type. These include: triggering systemic inflammation and clearance of activated platelets via splenic/liver macrophages and/or phagocytosis by neutrophils such as the case in influenza and rhinoviruses,[5] suppressing platelet production or enhancing platelet destruction such as the case in herpes and simian viruses,[5] and anti-viral antibodies cross-reacting with platelet surface integrins such as the case in adenovirus (platelet integrin GPIIb/IIIa).[5,7] Platelets were found to express the Coxsackie adenovirus receptor (CAR); in-vitro and in-vivo studies showed direct adenovirus-platelet interactions, followed by platelet activation as evidenced by increased expression of P-selectin with subsequent formation of platelet-leukocyte aggregates and expression of leukocytes and endothelial cells' activation markers.[8,9] Furthermore, the adenovirus-induced thrombocytopenia was found to be dependent on von Willebrand factor (VWF) since

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VWF-knockout (KO) mice did not show thrombocytopenia when injected by the virus.[8]

For thrombocytopenia associated with severe acute respiratory syndrome-coronavirus (SARS-CoV), the most closely related virus to COVID-19, multiple possible mechanisms have been suggested including the development of autoantibodies or immune complexes mediating clearance, direct infection of hematopoietic stem/progenitor cells and the megakaryocytic lineage via CD13 or CD66a resulting in decreased production of platelets, increased thrombomodulin levels leading to pathologic activation of the coagulation pathway and consumption of platelets, and increased plasma concentrations of tissue-plasminogen activator reflecting increased fibrinolysis.[10,11] Chen et al found that patients with SARS had significantly lower lymphocyte and platelet counts, and significantly higher soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble Fas ligand (sFasL) levels compared to healthy patients.[12] However, it remains unclear whether the apoptosis pathway is responsible for the reduced blood cell counts or whether sFasL and sVCAM-1 reflect vascular or tissue damage.[12] Researchers have also provided evidence that dysregulation of the urokinase pathway contributes to SARS-CoV pathogenesis.[13] Gralinski et al demonstrated a protective role for *Serpine1*, an inhibitor of the urokinase pathway, by showing that *Serpine1* knockout mice infected with SARS-CoV had increased fibrinolytic activity in their lungs and a decreased inflammatory response compared to wild-type mice.[13] Citing evidence from previous literature on SARS-CoV infection, Tang et al discusses a possibility of dysregulation of the urokinase pathway and provides evidence of fibrinolysis with COVID-19 deaths.[1]

To date, it is unclear what the exact mechanism of COVID-19 induced thrombocytopenia is. We don't know if this is a direct platelet-COVID-19 virus interaction or part of the sepsis-induced DIC. Is this interaction beneficial for the host as a trial to clear the viral pathogen or for the virusovercoming innate immunity? Is there a specific platelet ligand that COVID-19 binds to? What we do know is that COVID-19 belongs to the same lineage of coronaviruses as SARS-CoV, so it may be helpful to look at the mechanism behind SARS-CoV to guide COVID-19 studies while also keeping in mind that there are significant differences between SARS-CoV and COVID-19.[14] Compared to SARS-CoV, COVID-19 spike proteins have at least 10 times greater affinity for the human angiotensin-converting enzyme 2 (ACE2), a common host cell receptor shared between the two viruses.[14] Furthermore, Wrapp et al demonstrated that three different antibodies known to bind to the SARS-CoV spike protein failed to bind to COVID-19, suggesting the uniqueness of the novel coronavirus.[14]

A simple algorithm for the management of COVID-19 coagulopathy has just been reported. This is only based on supportive therapy, given the currently limited knowledge of the pathophysiology of DIC in COVID-19.[15] An understanding of the innate immune response and interrelated hemostatic mechanisms as critical initial response to COVID-19 infection is needed.[16] Additional research is warranted to elucidate the causal and pathophysiologic mechanisms of DIC and thrombocytopenia associated with COVID-19 with insight into the innate immune response to this virus. As the COVID-19 pandemic continues to evolve, research into these matters would be of utmost importance.

CONFLICTS OF INTEREST

All authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

AA gathered literature and wrote the manuscript. MO developed the plan and rationale for the letter, gathered literature and wrote the manuscript.

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Venous thromboembolism in COVID-19 patients

Dear Editor,

We read with interest the study published by Tang et al[1] in a recent issue of the *Journal of Thrombosis and Haemostasis*. In this retrospective analysis, conducted at the Tongji Hospital of Wuhan, China, it is reported that heparin treatment reduces mortality in subjects affected by severe COVID-19 who have "sepsis-induced coagulopathy." The definition of severe COVID-19 was the presence of at least one of the following: respiratory rate ≥30 breaths/minute, arterial oxygen saturation ≤93% at rest; PaO2/FiO2 ≤300 mm Hg. The authors of this study also reported that, among subjects not treated with heparin, mortality raised accordingly with D-dimer levels. Of note, patients that received heparin in this study were mostly treated with enoxaparin, at the thromboprophylactic dose of 40-60 mg/day, for at least 7 days.

We are surprised that only 22.0% of the population analyzed by Tang and colleagues (99 patients on a total of 449) received anticoagulant therapy for the prevention of venous thromboembolism (VTE). Indeed, patients hospitalized for COVID-19, and in particular those with a "severe" disease, are by definition at increased risk for VTE. Considering that these patients had respiratory failure, were likely bedridden for oxygen supplementation, and had an acute respiratory infection, their PADUA score[2] was necessarily ≥ 4, without even taking into account the possibility that some of them could have cancer, history of previous VTE, and age >70 years. Based on this, it is possible to hypothesize that, among the 350 patients that did not receive heparin (or were treated for fewer than 7 days), some developed pulmonary embolism (EP), which could have contributed to mortality in this group. This hypothesis is strengthened by the fact that mortality correlates with D-dimer levels among heparin non-users, although we are aware that high D-dimer levels may be due to many factors in COVID-19 patients and do not necessarily depend on the presence of VTE.

It would be helpful to know whether heparin users and non-users differed in terms of PADUA score. Also, it would interesting if the authors could retrospectively reanalyze their study population to determine how many patients were screened for VTE by ultrasonography of the legs and/or computed tomography (CT) scan pulmonary angiography, and assess whether VTE was more frequent among subjects who did not receive thromboprophylaxis with heparin, compared to heparin-treated individuals.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in association with this study.

AUTHOR CONTRIBUTIONS

Angelo Porfidia and Roberto Pola equally contributed to this article. Both authors discussed, commented, and finally approved the manuscript.

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