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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Editorial

Hematologic Consequences of the Coronavirus Crisis—Focus on Relevant Clues and Complications for the Perioperative Cardiothoracic and Vascular Community

THE CORONAVIRUS pandemic is a global crisis and has led to a surge in hospital-based care for severe coronavirus disease 2019 (COVID-19).[1-5] The unique considerations for severe COVID-19 have resulted in agile adaptation in the clinical arena, including graduate medical education, echocardiography, perioperative care, critical care, and extracorporeal membrane oxygenation.[6-12]

The purpose of this freestanding editorial is to highlight the hematologic consequences of the COVID-19 pandemic as they provide clues and challenges for the delivery of high-quality patient care. These features can improve the design of best practices to navigate this crisis creatively. The provided references can also assist leaders in their management of the pandemic at their respective institutions.

Consider the Complete Blood Count

The white blood cell response to coronavirus infection is characterized by lymphopenia.[13,14] The development of lymphopenia is nearly universal in clinically significant COVID-19, with an observed incidence range of 80% to 100%.[13-15] The degree of the lymphopenic response may significantly correlate with the severity of clinical infection.[14,15] The extent of the lymphopenia has significantly predicted the risks of admission to the intensive care unit, development of acute respiratory distress syndrome, and mortality.[13-18]

There appear to be multiple mechanisms for this lymphopenic phenotype in COVID-19. The first mechanism is that coronavirus can infect and directly destroy lymphocytes because they express the viral-binding protein on their surface membrane, namely angiotensin-converting enzyme 2.[19,20] A second mechanism for lymphopenia may be increased lymphocytic apoptosis due to the cytokine storm that may accompany infection with coronavirus.[7,21] This cytokine storm may also result in atrophy of lymphoid reserves, including the spleen, and impair lymphocyte levels.[22] A third mechanism for lymphopenia may be decreased proliferation from significant acidosis associated with severe COVID-19.[3-5,23]

Beyond lymphopenia, recent evidence from multiple clinical trials has suggested that thrombocytopenia is not only common but is very often associated with severe COVID-19.[24] Although the severity of the thrombocytopenia may at times correlate with the clinical severity of coronavirus infection, there may also be a platelet spike in the setting of a pronounced cytokine storm.[24] This relative platelet excess may result in an elevated platelet-to-lymphocyte ratio that appears to be an independent predictor for prolonged hospitalization and adverse clinical outcomes in COVID-19.[24-26] These platelet abnormalities may also have a role in the disordered coagulation that may accompany COVID-19, and that is explored further in the following section.

Consider the Coagulation System

Recent reports have demonstrated that COVID-19 may be complicated by thrombotic events in a variety of vascular beds, accompanied by markedly elevated D-dimer levels.[26-30] This hypercoagulability may precipitate both arterial and venous thrombosis. Ischemic stroke, myocardial infarction, deep venous thrombosis, pulmonary embolism, and line-associated thrombosis have been described.[28-30] A retrospective cohort study of 388 patients in Milan reported a cumulative rate of thromboembolic events of 21% in all hospitalized patients and 27.6% in patients receiving critical care.[29] A Dutch study reported an incidence of thromboembolic events in 31% of ICU patients.[30] However, the concerns about thrombosis in COVID-19 are not limited to overt thromboembolic events.[26] The pattern of preserved pulmonary compliance and profound hypoxemia in severe COVID-19 has led to speculation that pulmonary microvascular thrombosis may be a significant contributor to respiratory failure in this setting.[31,32] If pulmonary thrombotic burden is critical, it could lead to

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ventilation–perfusion mismatch and significant hypoxemia. Indeed, because thrombotic risk increases with age, thrombotic events could partially explain the age-associated mortality of COVID-19.[33] Given these risks of thrombosis, therapeutic anticoagulation in COVID-19 has been suggested as part of clinical management.[32-34]

The laboratory findings in COVID-19 include elevated D-dimers, suggesting high fibrinogen turnover.[26-28] Furthermore, D-dimer levels predict not only clinical severity but also mortality.[34] These levels may be as high as 10 times the normal levels in severe COVID-19.[32-34] Although these D-dimer levels can be remarkably high, further features of disseminated intravascular coagulation may not be present.[35-37] The fibrinogen levels are elevated, thrombocytopenia is not always present, and the prothrombin and activated partial thromboplastin times are either normal or minimally elevated.[38] Although antiphospholipid antibodies have been observed in this setting, this is not a uniform finding.[38,39] Furthermore, although disseminated intravascular coagulation typically presents as a mix of thrombosis and bleeding, the coagulation disturbance in COVID-19 appears to be primarily thrombotic.[26-29]

Because of these features, increased testing with thromboelastography has been explored to further characterize the prothrombotic effects of COVID-19.[38] The reported coagulation profile in this setting includes shortened clot times, increased maximum amplitude, and delayed clot lysis with a contact pathway initiator.[38] In addition to elevated fibrinogen and D-dimer levels, factor VIII and von Willebrand factor levels were also elevated, and antithrombin levels were mildly decreased to about 75% of normal.[38]

These findings provide further evidence that the microvascular thrombosis in severely ill patients with COVID-19 is often not consistent with disseminated intravascular coagulation that may accompany severe sepsis.[39-41] The clinical and laboratory evidence previously described suggest that the microvascular thrombosis in COVID-19 patients has many distinct differences that may also offer some clues about the mechanism of the disease process. The first observation is that it does not exhaust fibrinogen stores, which suggests that the normal hemostatic regulatory mechanisms can limit "runaway" coagulation activation.[38] The thrombosis that occurs in COVID-19 is probably the result of multiple foci of triggered coagulation. The second observation is that thrombocytopenia may not always be present, suggesting alternative drivers for this thrombotic disorder, including viral endothelial damage and marked complement activation.[20,26,31-32,36]

Mechanisms beyond complement activation must also be considered for the thrombotic disorder in COVID-19. The elevated fibrinogen and factor VIII levels could also lead to thrombosis.[38] However, these proteins are both acute phase reactants, and therefore their elevated levels alone are unlikely to explain the differences in thrombosis between COVID-19 and other severe inflammatory states.[42] The prothrombotic features of COVID-19 may also be triggered by damage-associated molecular patterns such as neutrophil extracellular traps.[43] These molecules contribute to disordered coagulation in inflammatory states through monocyte activation to link inflammation and thrombosis.[41,43,44] Neutrophil extracellular traps have been observed in COVID-19 plasma and may offer not only an explanation for the thrombotic features of COVID-19 but also a therapeutic targer.[45-48]

As the pandemic progresses, patients with COVID-19 may require cardiac surgery.[1-2] Given the importance of hemostasis in cardiac surgery and the disordered coagulation system in COVID-19, there may be important implications for the perioperative management of cardiac surgical patients. An important example of this is perioperative anticoagulation monitoring. Because factor VIII levels may at times be markedly elevated in COVID-19, this may lead to artificially lower clotting times in contact-dependent assays such as the activated clotting time and the partial thromboplastin time.[49] This resulting over-anticoagulation may precipitate bleeding complications. Adequate anticoagulation must, however, be maintained both for cardiopulmonary bypass and extracorporeal membrane oxygenation, given the risks of hypercoagulability in this setting.[2-3,50,51] Disordered coagulation in COVID-19 is a key consideration that contributes to large and small vessel thrombosis. These thrombotic complications contribute to mortality and have unique features that require further investigation to advance clinical management.

Consider the Challenges With Blood Product Supply

The COVID-19 pandemic has precipitated an acute shortage of blood products, mostly from reduced blood donation due to social distancing.[51-53] This has prompted a series of public awareness programs to restore blood donation in a safe and appropriately adapted fashion to maintain a national blood supply.[51-53] Further attention to managing demand has also been advocated as an important strategy to navigate this crisis.[53] The measures that could ease demand include higher transfusion thresholds and multimodal guideline-driven perioperative blood management.[54-56] These measures have been covered in detail elsewhere in the journal for adult and pediatric cardiothoracic and vascular practice.[54-56] The priority through the pandemic is balance supply with demand in this space.

Conclusions

The hematologic response to COVID-19 significantly guides diagnosis and management in this challenging disease. The prothrombotic vascular milieu is likely multifactorial but should be considered in tailored patient management. A sustained focus on infection control and blood management remains essential.

Conflict of Interest

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References

1 Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease (COVID-19): Challenges and recommendations. Lancet Respir Med 2020;8:506–17.
2 He Y, Wei J, Bian J, et al. Chinese Society of Anesthesiology expert consensus on anesthetic management of cardiac surgical patients with suspected or confirmed coronavirus disease 2019. J Cardiothorac Vasc Anesth 2020;34:1397–401.
3 Augoustides J.G.Extracorporeal membrane oxygenation—crucial considerations during the coronavirus crisis [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.03.060. Accessed May 28, 2020.
4 World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected—Interim guidance. Available at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed May 12, 2020.
5 Augoustides JG. Critical care during the coronavirus crisis—Challenges and considerations for the cardiothoracic and vascular anesthesia community [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.04.021. Accessed May 28, 2020.
6 Zhao S, Ling K, Yan H, et al. Anesthetic management of patients with suspected or confirmed 2019 novel coronavirus infection during emergency procedures [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.02.039. Accessed May 28, 2020.
7 Augoustides JG. Cardiovascular consequences and considerations of coronavirus infection—Perspectives for the cardiothoracic anesthesiologist and intensivist during the coronavirus crisis [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.04.001. Accessed May 28, 2020.
8 Augoustides JG. Perioperative echocardiography: Key considerations during the coronavirus pandemic. J Cardiothorac Vasc Anesth 2020;34:1416–8.
9 Augoustides JG. Perioperative echocardiography during the coronavirus crisis – considerations in pediatrics and congenital heart disease [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.04.022. Accessed May 28, 2020.
10 Weixia Li, Huang J, Guo X, et al. Anesthesia management and perioperative infection control in patients with the novel coronavirus [e-pub ahead of print]. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.03.035. Accessed May 28, 2020.
11 Tan Z, Phoon PHY, Zeng LA, et al. Response and operating room preparation for the COVID-19 outbreak: A perspective from the National Heart Centre Singapore. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.03.050. Accessed May 28, 2020.
12 Al Ghofaily L, Feinman J, Augoustides JG. Fellowship training in adult cardiothoracic anesthesiology: Navigating the new educational landscape due to the coronavirus crisis. J Cardiothorac Vasc Anesth. doi: 10.1053/j.jvca.2020.04.019. Accessed May 28, 2020.
13 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
14 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
15 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9.
16 Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. doi: 10.1001/jamainternmed.2020.0994. Accessed May 30th 2020
17 Fan BE, Chong VCL, Chan SSW. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020;95:E131–4.
18 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054–62.
19 Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8.
20 Augoustides JG, Liang WG, Chen FW, et al. The renin-angiotensin-aldosterone system in coronavirus infection—Current considerations during the pandemic. J Cardiothorac Vasc Anesth 2020;34:1717–9.
21 Liao YC, Liang WG, Chen FW, et al. IL-19 induces production of IL-6 and TNF−alpha and results in cell apoptosis through TNF-alpha. J Immunol 2002;169:4288–97.
22 Chan JF, Zhang AJ, Yuan S, et al. Simulation of the clinical and pathological manifestations of coronavirus disease 2019 (COVID-19) in golden Syrian hamster model: Implications for disease pathogenesis and transmissibility. Clin Infect Dis. doi: 10.1093/cid/ciaa325. Accessed May 20th 2020
23 Fischer K, Hoffmann P, Voelkl S, et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 2007;109:3812–9.
24 Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020;506:145–8.
25 Qu R, Ling Y, Zhang YH, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. doi: 10.1002/jmv.25767. Accessed May 29th 2020
26 Terpos E, Ntanasis- Stathopoulos I, Elalamy J, et al. Hematological findings and complications of COVID-19. Am J Hematol. doi: 10.1002/ajh.25829. Accessed May 29th 2020
27 Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. doi: 10.1111/all.14238. Accessed May 28th 2020
28 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18:1023–6.
29 Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14.
30 Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 2020;191:148–50.
31 Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of 5 cases. Transl Res 2020;220:1–13.
32 Harenberg J, Favaloro E. COVID-19: Progression of disease and intravascular coagulation—Present status and future perspectives. Clin Chem Lab Med. doi: 10.1515/cclm-2020-0502. Accessed May 29th 2020
33 Wilkerson WR, Sane DC. Ageing and thrombosis. Semin Thromb Hemost 2002;28:555–68.
34 Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:1094–9.
35 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7.
36 Campbell CM, Kahwash R. Will complement inhibition be the new target in treating COVID-19 related systemic thrombosis? Circulation 2020;141:1739–41.
37 Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: A position paper from the Italian Society of Thrombosis and Haemostasis. Blood Transfus 2020;18:167–9.
38 Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 10.1111/jth.14850. Accessed May 28th 2020.
39 Connell NT, Battinelli EM, Connors JM. Coagulopathy of COVID-19 and antiphospholipid antibodies. J Thromb Haemost. doi: 10.1111/jth.14893. Accessed May 30th 2020.
40 Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:E38.
41 Semeraro N, Ammollo CT, Semeraro F, et al. Coagulopathy of acute sepsis. Semin Thromb Hemost 2015;41:650–8.
42 Kamphuisen PW, Eikenboom JC, Bertina RM. Elevated factor VIII levels and the risk of thrombosis. Arterioscler Thromb Vasc Biol 2001;21:731–8.

43 Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. Anesthesiology 2020;132:1238–45.
44 Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol 2018;18:134–7.
45 Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020;5:138999.
46 Mozzini C, Girelli D. The role of neutrophil extracellular traps in COVID-19: Only an hypothesis or a potential new field of research. Thromb Res 2020;191:26–7.
47 Magro C, Mulvey JJ, Berlin D, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med 2020;217: e20200652.
48 Golonka RM, Saha P, Yeoh BS, et al. Harnessing innate immunity to eliminate SARS-CoV-2 and ameliorate COVID-19 disease. Physiol Genomics 2020;52:217–21.
49 Mitsuguro M, Okamoto A, Shironouchi Y, et al. Effects of factor VIII levels on the APTT and anti-Xa activity under a therapeutic dose of heparin. Int J Hematol 2015;101:119–25.
50 Giacomelli E, Dorigo W, Fargion A, et al. Acute thrombosis of an aortic prosthetic graft in a patient with severe COVID-19-related pneumonia. Ann Vasc Surg. doi: 10.1016/j.avsg.2020.04.040. Accessed May 28th 2020.
51 Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter, prospective cohort study. Intensive Care Med 2020;46:1089–98.
52 Pagano MB, Hess JR, Tsang HC, et al. Prepare to adapt: Blood supply and transfusion support during the first 2 weeks of the 2019 novel coronavirus (COVID-19) pandemic affecting Washington state. Transfusion 2020;60:908–11.
53 Gehrie EA, Frank SM, Goobie SM. Balancing supply and demand for blood during the COVID-19 pandemic. Anesthesiology. doi: 10.1097/ALN.0000000000003341. Accessed May 30th 2020.
54 Faraoni D, Meier J, New HV, et al. Patient blood management for neonates and children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2019;33:3249–63.
55 Boer C, Meesters M, Milojevic M, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. J Cardiothorac Vasc Anesth 2018;32:88–120.
56 Dhir A, Tempe DT. Anemia and patient blood management in cardiac surgery: Literature review and current evidence. J Cardiothorac Vasc Anesth 2018;32:2726–42.