

Platelets in Coronavirus Disease 2019

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In December 2019, the first cases of infection with a novel human microorganism, now officially defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported in Wuhan, China.¹ On April 1, 2020, as we write, more than 800,000 cases of the novel coronavirus disease 2019 (COVID-19) have been reported worldwide, with more than 40,000 COVID-19-related deaths.²

Studies have reported disturbed coagulation in COVID-19 patients, including prolonged prothrombin time,^{3,4} decreased antithrombin,³ and increased fibrin degradation products such as D-dimer.^{3–7} This implies increased risk of thromboembolic disease, as well as bleeding and, for the most serious cases, development of disseminated intravascular coagulation (DIC), which, in one case series, was reported in as many as 71% of nonsurvivors of COVID-19.⁵

This commentary explores the potential role of platelets in COVID-19, including the link between thrombocytopenia and disease severity and the considerations for the potential role for platelet function and/or platelet activation testing in COVID-19 patients.

Platelet Count and Disease Severity in COVID-19

Thrombocytopenia is reported in 5 to 40%^{4,6,8,9} of COVID-19 patients and appears to be associated with more severe disease. A meta-analysis by Lippi et al,¹⁰ including nine studies with more than 1,700 COVID-19 patients in total, reported a significant association between thrombocytopenia at admission and severe disease. Platelet counts were significantly lower in severely ill patients (weighted mean difference: $-31.5 \times 10^9/L$) and were associated with increased mortality in a subgroup analysis. This is supported by additional studies^{11–13}; Mo et al reported lower platelet counts in patients with refractory disease ($n = 85$), defined as a lack of clinical and radiological

remission after 10 days, than in patients with remission after 10 days ($n = 70$) (mean with interquartile range [IQR]: 159 [119–202] vs. 179 [146–219] $\times 10^9/L$).¹¹ In a study of 107 patients, Wang et al reported lower platelet count in non-survivors ($n = 19$) than survivors (mean with IQR: 122 [83–178] vs. 178 [139–207] $\times 10^9/L$; $p < 0.01$).¹² It should be noted that the study by Wang et al is still in the process of completing peer review. Finally, a study by Tang et al including 449 patients found platelet count to be negatively correlated with 28-day mortality in a multivariate analysis.¹³

However, the majority of even severely ill COVID-19 patients exhibit only mild thrombocytopenia. One case series ($n = 62$) reported that only 5% of patients had platelet counts $< 100 \times 10^9/L$,¹⁴ and in 69 patients from Singapore, no patients had platelet counts $< 100 \times 10^9/L$ at admission.⁹ In studies reporting on platelet count in COVID-19, mean platelet counts ranged from ~ 160 to $215 \times 10^9/L$ in COVID-19 patients in general^{4,6–8,11,12,15–18} to 120 to $200 \times 10^9/L$ in severely ill patients.^{4,6,7,11,12,15–17,19,20} Tang et al reported on the association between coagulopathy and mortality in 183 COVID-19 patients.⁵ Of the 21 patients who did not survive, 12 (57%) had platelet counts $< 100 \times 10^9/L$.

Based on these data, it appears that while mild thrombocytopenia is a common finding in COVID-19 patients, a platelet count of $< 100 \times 10^9/L$ seems rare and should be interpreted as an indicator of present or developing coagulopathy. This could help identify patients who could benefit from thromboprophylaxis.¹³

Interestingly, Qu et al demonstrated an association between high platelet counts and poor prognosis.²¹ The authors found that severely ill COVID-19 patients exhibited higher peak platelet counts than their nonseverely ill peers during hospital admission and that the platelet-to-lymphocyte ratio during platelet peak was markedly higher in severely ill patients. However, the study included 30 patients in total, with

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only 3 with severe disease. Thus, these findings should be replicated in other cohorts before the platelet-to-lymphocyte ratio can be better investigated as a prognostic factor. Furthermore, low lymphocyte counts have consistently been found associated with worse prognosis,^{4,6} and this may be the explanation for the findings described by Qu et al, more than the high platelet counts per se.

Mechanisms behind Thrombocytopenia in COVID-19: A Role for Platelet Activation?

Platelets are known to interact directly with several different types of virus through surface integrins, P-selectin, and toll-like receptors, as recently reviewed in detail in this journal by Page and Pretorius.²² Regarding interactions between SARS-CoV-2 and platelets, however, current knowledge is sparse. Some lessons may be learned from the SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) outbreaks in 2002 to 2003 and 2012, where similar findings have been described of thrombocytopenia, predominantly mild, in 30 to 50% of patients.²³⁻²⁶

Mechanisms behind thrombocytopenia in the 2003 SARS-CoV infection have been reviewed by Yang et al.²⁷ These may include both a direct influence of the virus on hematopoiesis and megakaryocyte maturing, and an increased platelet adhesion and activation and subsequent platelet consumption in the microcirculation of damaged lung tissue.²⁷ Platelet activation in the pulmonary microcirculation could not only contribute to the procoagulant activity described in COVID-19 patients but also aggravate damage to the lung parenchyma and contribute to the respiratory distress and frequent need for mechanical ventilation, which is a hallmark of severe COVID-19. Finally, hyperinflammation appears to be a prominent feature of severe COVID-19, as increased serum levels of ferritin, interleukin-6, and other proinflammatory cytokines have been reported and are linked to worse prognosis in COVID-19.^{4,7,28,29} This could also contribute to platelet activation in COVID-19.³⁰

These data open interesting perspectives for the role of platelet activation and for possible benefits of antiplatelet agents in COVID-19. However, these questions should be explored in future research since, to the best of our knowledge, no study has yet reported on platelet activation in COVID-19 patients.

Conclusion

To conclude, mild thrombocytopenia is a common finding in COVID-19, and thrombocytopenia is linked with more severe disease and mortality. Platelet counts $< 100 \times 10^9/L$ should lead the clinician to suspect the development of complications in the COVID-19 patient, for example, DIC.

Our current knowledge of other human coronaviruses suggests that ongoing platelet activation in pulmonary and other tissues could be present in COVID-19 and could hence contribute to increased procoagulant activity observed in COVID-19. However, to the best of our knowledge, platelet

function testing has not been performed in COVID-19 patients so far. This is a focal point for future research to increase our understanding of the pathophysiology of COVID-19 and explore possible treatment targets.

Conflicts of Interest

Dr. Hvas reports grants from CSL Behring and other fees from CSL Behring, Boehringer Ingelheim, and Bayer, outside the submitted work.

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