

# Is COVID-19–Induced Platelet Activation a Cause of Concern for Patients with Cancer?

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## ABSTRACT

Patients with cancer are more susceptible to be infected by SARS-CoV-2 and develop severe outcomes including ICU admittance, mechanical ventilator support, and a high rate of mortality. Like mid-to late-stage cancer, SARS-CoV-2 infection is associated with platelet hyperactivity, systemic inflammation, thrombotic complications, and coagulopathy. Platelets also promote cancer cell

growth, survival in circulation, and angiogenesis at sites of metastases. In this article, we will discuss the potential for platelets in the development of systemic inflammation and thrombosis in SARS-CoV-2–infected patients with cancer, with the concern that the platelet-induced pathogenic events are likely magnified in cancer patients with COVID-19.

## Introduction

Severe acute respiratory syndrome-coronavirus (SARS-CoV-2) has infected over 36 million people worldwide, resulting in over 1 million deaths primarily of respiratory, cardiac, and kidney failure. The burden and the degree of severity of coronavirus disease-19 (COVID-19) varies among individuals with certain subgroups, and patients with cancer are disproportionately impacted by the disease.

The pathogenic mechanism of COVID-19 is still being explored with evidence that the viral infection is associated with severe venous and arterial thromboembolic complications and a hypercoagulable state that compromises blood flow to infected organ systems. Blood platelets promote the formation of microthrombi (blood clots) and support the systemic inflammatory process. Besides these classical roles for platelets, we had previously presented compelling evidence from the literature that support a role of platelets in the multiple stages of cancer progression, in the “Controversy and Consensus” section of this journal (1). This includes the initial induction of epithelial-to-mesenchymal transition resulting in dysplasia; the promotion of the growth of cancer cells in the primary tumor; the translocation of cancer cells across endothelial membranes to become circulating tumor cells (CTC); the formation of neutrophil/platelet complexes called neutrophil extracellular traps (NET) in the blood thereby protecting the CTCs from immune attack and associated apoptosis (anoikis); and ultimately the extravasation of CTCs across endothelial membranes to distant tissue sites where cancer cell growth is supported by platelet

induced angiogenesis, a process mediated by the release of VEGF from platelet alpha granules.

Thus, platelets are uniquely positioned at an intriguing nexus between COVID-19–induced pathology and cancer progression. In this article, we will review evidence that COVID-19 pathogenesis is linked with platelet hyperactivity and the disproportionate representation of cancer patients to SARS-CoV2 infection resulting in severe disease. We will then discuss the implications of aberrant platelet physiology in the context of patients with cancer infected with the virus.

## SARS-CoV-2 Infection Promotes Platelet Activation and Thrombotic Events

One of the hallmarks of SARS-CoV-2 infection is COVID-19 associated coagulopathy with aberrant alterations in coagulation, inflammation, and thrombosis. Indeed, disseminated intravascular coagulation, a condition wherein blood clots are formed throughout the body along with bleeding, are reported in a majority of patients that died of SARS-CoV-2 infection (2). The propensity of the virus to support thrombotic events could be related to its ability to alter the physiology of endothelium, immune cells, and platelets.

For the latter cell type, evidence is mounting that SARS-CoV-2 virus can induce both the local and systemic activation of platelets, including the release of inflammatory cytokines that play a role in both the propagation of COVID-19 and the generation of the cytokine storm that contributes to the lethality of the disease. Zaid and colleagues studied platelet function in SARS-CoV-2–infected patients experiencing mild and severe disease and reported that platelets from both groups of patients were in a hyperactivated state, compared with platelets of healthy (non-COVID) controls (2). Specifically, platelets from COVID-19–positive patients displayed increased aggregation, adhesion, and microvesiculation to subthreshold concentration of thrombin. It has also been reported that SARS-CoV-2 RNA was detected in platelets from 15% to 20% of COVID-19–positive patients, suggesting possible platelet-mediated uptake of the viral RNA. Manne and colleagues studying platelets collected from 41 COVID-19–infected patients from intensive care units (ICU) and non-ICU settings also reported increased P-selectin expression (a marker of platelet activation) elevated platelet-leukocyte aggregates, faster platelet aggregation, and increased spreading of platelets over fibrinogen/collagen–coated surfaces, compared with the function

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of platelets collected from noninfected controls (3). Interestingly, SARS-CoV-2 infection altered platelet transcriptomics; SARS-CoV-2 RNA was detected in a subset of COVID-19–positive platelets, and that administration of the antiplatelet agent, aspirin reduced COVID-19–induced platelet hyperactivity. Zhang and colleagues performed a comprehensive study with 166 healthy volunteers, 60 non-COVID-19 hospitalized patients, and 241 COVID-19 patients and reported platelet hyperreactivity based on increased integrin  $\alpha_{IIb}\beta_3$  activation and P-selectin expression in COVID-19–positive patients (4). More importantly, *in vitro* studies demonstrated that addition of live SARS-CoV-2 virus or the SARS-CoV-2 spike S1 protein to platelets from healthy subjects, dose-dependently potentiated platelet functions (adhesion, aggregation, and secretion) in response to platelet agonists. Finally, purified SARS-CoV-2 spike S1 protein induced *in vivo* thrombosis in wild-type mice transfused with platelets from transgenic mice expressing human angiotensin-converting enzyme 2 (ACE2), suggesting that ACE2 is required for the platelet response. The latter finding was based upon evidence that platelets collected from COVID-19–positive patients express ACE2 and transmembrane protease, serine 2 (TMPRSS2), which are required for viral entry into host cells. To our knowledge, these more controversial findings of Zhang and colleagues have yet to be confirmed. These observations indicate that SARS-CoV-2 virus can alter platelet transcriptomics, elevate platelet-leukocyte aggregates, promote and/or potentiate agonist induced platelet adhesion, aggregation, secretion, and facilitate thrombus formation. These intrinsic changes in platelet physiology induced by the SARS-CoV-2 infection that support microthrombi and inflammatory milieu may also have implications in cancer biology.

### SARS-CoV-2 Infection Disproportionately Impacts Patients with Cancer

As the COVID-19 pandemic is known to take a serious and potentially-life threatening course in older patients with a number of comorbidities, clinical investigators have recently become aware that patients with cancer are particularly prone to SARS-CoV-2 infection and are likely to develop severe critical disease. The vulnerability of patients with cancer to SARS-CoV-2 infection is highlighted in a study wherein the rate of SARS-CoV-2 infection was 0.37% in the general Wuhan population as compared with 0.79% among hospital admitted cancer patients during the same time period (5). Among the 1,542 patients with cancer studied, COVID-19 incidence was highest for patients with non-small cell lung cancer (NSCLC). The all-cause mortality of patients with cancer identified from The COVID-19 and Cancer Consortium (CCC19) registry within 30 days of COVID-19 diagnosis was as high as 13%.

In a systemic review of 22 studies on 1,008 patients with cancer ElGohary and colleagues reported that patients with cancer infected with SARS-CoV-2 had a significantly higher rate of: mortality (21%); development of severe disease (45%); ICU admittance rate (14.5%); and patients requiring mechanical ventilation (11%) than cancer-free SARS-CoV-2–infected subjects (6). It should be noted that the statistics of other studies varied (e.g., mortality ranging from 9% to 33%), but the trend remained that patients with cancer with COVID-19 were one of the groups at greatest risk (2–3 fold vs. noncancer subjects with COVID-19) of developing serious life-threatening disease. Similar findings by Dai and colleagues on 105 patients with cancer with COVID-19 versus 536 age-matched noncancer subjects with

COVID-19 admitted to 14 hospitals in Wuhan Province also concluded that patients with cancer had significantly more severe disease outcome and mortality rates (3-fold higher than COVID-19 patients without cancer; ref. 7). Specifically, hematologic and lung cancer patients with advance stage metastatic cancer had the highest risk of death, ICU admission, and dependence on mechanical ventilation support. In a study that matched 232 patients with COVID-19–positive cancer versus 519 age-matched COVID-19–positive noncancer patients from 9 hospitals, Tian and colleagues reported that patients with cancer had 2-fold risk of developing severe disease versus noncancer patients (8). Furthermore, cancer stage and elevated circulation cytokines (notably IL6) and reduced CD4<sup>+</sup> T cells were indicators of poor outcome. The above studies reported that the actual cause of death of COVID-19–positive patients with cancer included acute respiratory distress syndrome (ARDS), sepsis, multi-organ failure, myocardial infarction, pulmonary embolism, and hematologic or solid tumor malignancy (which was particularly high in patients with lung cancer). It was also unclear whether COVID-19–positive patients with cancer should continue a treatment protocol, as it was reported that chemotherapy, immunotherapy, and surgery generally appeared to worsen the course of the disease (8). Patients with cancer who had surgery or immunotherapy 40 days prior to COVID-19 symptoms also had higher rates of death, higher chances of ICU admissions with the use of ventilators, compared with COVID-19–positive noncancer patient (7). Despite the heterogenous nature of diverse populations of cancer patients and their response to SARS-CoV-2 infection, the emerging epidemiologic studies suggest an adverse outcome for patients with cancer with COVID-19 with potential implications for therapy.

### Potential Impact of SARS-CoV-2 Induced Altered Platelet Physiology in Patients with Cancer

Besides the known immunocompromised state of some patients with cancer, investigators have yet to determine how preexisting cancer may exacerbate the severity of infection and the outcome in patients with cancer with COVID-19. One possibility that should be considered is that patients with cancer infected with COVID-19 have a higher burden of inflammatory and thrombotic complications induced by hyperactive platelets. This view is built on evidence that place platelets at a nexus between COVID-19 and malignancy. The spike protein of SARS-CoV-2 and the state of malignancy can both activate platelets with implications related to disease outcome for patients with cancer with COVID-19 infection. Cytokine storm is a central feature of severe COVID-19 pathophysiology and platelets contribute directly to the cytokine load in plasma. Indeed, platelets from COVID-19–positive subjects are more sensitized to release cytokines that support malignancy such as TGF $\beta$ , IL1 $\beta$ , and INF $\gamma$  (2). Platelets also promote NET formation and COVID-19–positive subjects displayed increased NETs (2). NETs can trigger thrombosis, activate coagulation, facilitate cytokine release, and support platelet microthrombi that occlude vessels to propagate organ injury. Because NETs also protect circulating tumor cells from immune attack, increased NET formation induced by SARS-CoV-2 could adversely impact patients with cancer by promoting the development of metastatic disease. Platelets play a role in venous thromboembolism (VTE) and VTE represents the most frequent complication reported in hospitalized patients with COVID-19. Compared with the general population, patients with cancer have 4–7 fold increased risk of VTE.

However, it should be noted that one retrospective study reported, the cumulative incidence of thrombosis of hospitalized patients infected with COVID-19 at day 28 were not different between those with cancer versus the noncancer cohort. It should be noted they also reported that the incidence of key thrombotic events such as deep vein thrombosis, pulmonary embolism, and ischemic stroke were modestly increased in COVID-19-infected patients with cancer versus the noncancer group (9). Interestingly, the same study also reported that the overall survival period was significantly shorter in the group with active cancer, though the actual cause of death in COVID-19-infected patients with cancer was uncertain.

In a very recently published study, it was reported that the administration of low dose (81 mg) aspirin, which also has established antiplatelet and anticancer efficacy, has shown promise in reducing the severity and poor outcome by 43%–47% in hospitalized COVID-19 patients (vs. infected patients not taking aspirin; ref. 10). It will be of great interest, therefore, to determine the efficacy of aspirin and related platelet antagonists in the formulation of future drug cocktails to treat several sequelae of SARS-CoV-2 infection including thrombosis, inflammation, and cancer. Indeed, it has recently been announced that low dose (150 mg) aspirin will be evaluated along with other therapies in the Recovery Trial, a large British clinical trial to determine whether aspirin reduces the risk of blood clots in COVID-19 patients. In summary, observations that link platelets, COVID-19 and malignancy suggest the possibility that altered platelet physiology in SARS-CoV-2 infected patients with cancer could adversely exacerbate the progression and metastatic spread of cancer and a potential therapeutic role for anti-platelet agents in altering the course of the disease.

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## Conclusion

In our opinion, there is compelling evidence that cancer patients are more vulnerable to SARS-CoV-2 infection. They are more likely to generate severe disease, leading to higher rates of ICU admittance, mechanical ventilator support, and mortality within 30 days of COVID diagnosis. The precise underpinning mechanisms of these epidemiologic findings are likely to be multifactorial and complex. On the basis of the strong observations that SARS-CoV-2 infection activates platelet physiology, we posit that hyperactive platelets may provide detrimental features for thrombotic and inflammatory conditions in COVID-19-positive patients with cancer. The efficacy of antiplatelet agents like aspirin, which are effective in blocking the formation of microthrombi, that showed promise in ongoing COVID-19 studies should be expanded and explored in the treatment of patients with cancer infected with COVID-19.

## Authors' Disclosures

L.M. Lichtenberger reports being co-founder of and shareholder in PLx Pharma Inc. that is developing an aspirin formulation, which may have utility in the treatment of COVID patients, outside the submitted work. No disclosures were reported by the other authors.

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