Editorial Commentary

Severe COVID-19 outcomes and hematological cancers: the clot thickens—are platelets the culprit?

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The World Health Organization (WHO) estimates that global pandemic with severe acute respiratory syndrome-coronavirus (SARS-CoV-2) has infected over 767M people worldwide, resulting in 6.9M deaths as of June 2023. Within the population, cancer patients are more susceptible to SARS-CoV-2 infection *vs.* cancer-free individuals and have a far worse coronavirus disease 2019 (COVID-19) outcome and higher rate of mortality (1,2). The availability of COVID-19 vaccinations including all the primary series doses and boosters dramatically decreased mortality rate (3). Unfortunately, COVID-19 vaccines were less effective in certain cancer patients which likely accounts for a higher number of breakthrough infections (4,5). However, whether the type of cancer and/or the nature of ongoing anticancer therapy impacts the effectiveness of COVID-19 vaccine in cancer patients is still being explored.

To this end, an elegant article by Gong *et al.* in *JAMA Oncology* has extended our understanding of the nuance associated with COVID-19 breakthrough in vaccinated cancer patients, (with different cancer types and treatments) *vs.* cancer free individuals (6). This retrospective observational study captured medical records of all 14 million Ontario residents, with a focus on 289,400 individuals with cancer (both hematological-39,880 and solid cancers-248,520) and 1,157,600 cancer-free individuals, all of which had at least 2-rounds of vaccinations against COVID-19 (the majority being mRNA-based). Their study revealed that breakthrough infections (primary outcome) were modestly higher in hematologic cancer patient's *vs.* non-cancer controls, especially those undergoing active treatment with anti-CD20 antibody therapy. A similar trend in breakthrough infections was not observed in patients with solid cancer *vs.* non-cancer individuals, and a modest but significant difference was ascertained in breakthrough infections between hematologic *vs.* solid cancer patients.

Although not the primary outcome being studied, in our opinion, the most striking findings of this paper were as follows. Both hematologic and solid cancer patients had more severe COVID-19 disease outcomes *vs.* non-cancer controls. Particularly, blood cancer patients experienced a 2–3-fold increase in emergency room visits, hospitalization and mortality. Even more impressive was that both hematologic and solid cancer patients undergoing active cancer therapy further exacerbated COVID-19 associated outcome, especially those with blood cancer who had a 3–4-fold increase in ER visits, hospitalization and death rate *vs.* non-cancer controls. Anti-CD20 therapy was of particular concern in hematological cancer patients

due to the increasing hazard ratio of 12.31 for ER visits, 7.14 for hospitalizations and 6.28 for recorded deaths. Thus, compared to cancer-free individuals, hematological cancer patients fared worse with respect to breakthrough COVID-19 infection, and those undergoing active anti-CD20 therapy displayed higher COVID-19 severity and mortality.

Of the 39,880 patients with hematological cancer in the study, a vast majority (~70.4%) represents individuals with a diagnosis of either leukemia, myeloproliferative neoplasm, myelodysplastic syndrome, lymphoma, or multiple myeloma based on the International Classification of Diseases (ICD) codes in the Ontario Cancer Registry (OCR) with 10 years of the index date. Why such preexisting diagnosis of hematological cancer increased the severity and worsened the outcome of COVID-19 is yet to be fully understood. The vulnerability of hematological cancer patients to COVID-19 severity is thought to stem from the existing comorbidities including weakened immunity (immunocompromised) state. However, it is now apparent that besides dysregulated immunity, persistent inflammation, and enhanced thrombosis are also important facets of COVID-19 pathophysiology. Platelets are an anuclear cell type in the blood that can facilitate immunity, coagulation, inflammation, and thrombosis. Indeed, SARS-CoV-2 infection altered platelet transcriptomics, increased platelet-leukocyte interaction, promoted platelet activation, facilitated thrombus formation and thus directly contributed to COVID-19 severity (7-9). Moreover, SARS-CoV-2 vaccination blunted COVID-19 associated platelet activation, including platelet microvesiculation that facilitated coagulation; P-selectin exposure that allowed inflammation/thrombosis by engagement with neutrophils and activating neutrophil extracellular traps (NETs) (10). Based upon the evidence that platelets are in a hyper-active state in COVID-19 patients and in several clinical malignancies and/or in models of experimentally-induced cancer, we argued in a Commentary in 2021 that COVID-19-induced platelet activation may be a cause of concern for cancer patients (11). Specifically, certain facets of hyperactive platelet (patho)physiology including the ability to release local cytokines (8), engage neutrophils to NETs (8,12) and thus propagate heightened inflammatory state, which supports COVID-19 pathophysiology and malignancy (13). Consistent with this argument, Gong *et al.* (6) observed increased COVID-19 severity in cancer patients *vs.* cancer-free individuals. It is interesting to note that a subset of "hematological cancer" studied by Gong *et al.* (6) includes myeloproliferative neoplasms, wherein the bone marrow produces an excess of blood cells (red cells, white cells and platelets). Particularly, among the phenotype of myeloproliferative neoplasms with increased platelet count called essential thrombocythemia (ET), there was an increased susceptibility of ET associated thrombosis in these patients with COVID-19 (14). Similarly, a high risk of hospitalization was seen in a subset of myeloproliferative neoplasm (MPN) patients with COVID-19 diagnosis that displayed an heightened inflammatory state like increased neutrophil to lymphocyte counts (NLR) (15). It is thus possible that increased platelet/neutrophil/red cell numbers in myeloproliferative neoplasms, and/or increased platelet activation in other hematological cancers may trigger heightened inflammatory and/or thrombotic burden and thus increase COVID-19 severity in this cohort.

Another striking feature of the study by Gong *et al.* (6) was the increased COVID-19 severity in a subset (5.6%) of hematological cancer patients receiving anti-CD20 antibody therapy. Anti-CD20 antibody therapy depletes B cells and likely diminishes humoral immunity response to the COVID-19 spike protein, with reduced seropositive antibodies and increased patient vulnerability. However, anti-CD20 antibodies particularly, rituximab (used in the study) is also known to trigger the release of activated platelet-dependent chemokines like neutrophil-activating protein-78, monocytic chemoattractant protein-1 (MCP-1), RANTES (regulated on activation, normally T-cell expressed and secreted) (16). Furthermore, rituximab increases complement activation and cytokine release (17), and enhances activated NETs formation *in vitro* (18). Platelet-mediated release of cytokines (8), aberrant complement activation (19) and increased NETs (8,12) are all features observed in COVID-19 pathophysiology. Furthermore, platelet chemokines/cytokines (20), complement activation (21) and NETs (13) all have tumor promoting activity as well. It is currently unknown if anti-CD20 antibody therapy promotes a higher burden of inflammatory and thrombotic complications in cancer patients, in part, via the release of platelet chemokines/cytokines, complement activation and facilitating NETosis.

The study by Gong *et al.* has intrinsic limitations in part due to its reliance on a linked administrative database. Primarily, there is a lack of granular clinical data on hematological cancer including the stage of disease, whether the patients exhibit a degree of remission or relapse, the use of chemotherapy other than anti-CD20 antibody and whether any of the anti-cancer therapy was withdrawn in

the context of COVID-19. Indeed, Barbui *et al.* recently reported that COVID patients with myeloproliferative neoplasms had an alarming mortality rate (24%) after ruxolitinib was withdrawn (22). Nonetheless, this population based retrospective observational study (6) reveals that hematological cancer and those with anti-CD20 antibody therapy are more vulnerable to COVID-19 disease and outcomes. Such information will likely guide physicians and healthcare providers to prioritize this vulnerable subgroup of cancer patients for the armamentarium available to fight COVID-19. To researchers, this study raises new questions about the underpinning mechanisms and lays the foundation for new hypotheses. In the light of mounting evidence in the literature that suggests platelet hyperactivation can promote dysregulation of inflammation, thrombosis, and immunity in COVID-19 pathophysiology, it is but natural to hypothesize "are platelets the culprit in the increased COVID-19 severity in hematological cancer"?

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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