

# Thrombosis and Hemostasis Issues in Cancer Patients with COVID-19

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Coronavirus disease 2019 (COVID-19) is an infectious pandemic disorder caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a single-stranded RNA  $\beta$ -coronavirus. Virus particles that can be inhaled through the respiratory system and invade lung alveolar cells may cause a limited viral disease. However, in some patients, severe complications, including systemic inflammatory response syndrome, acute respiratory disease syndrome, multiple organ failure, and shock may develop. These presentations are particularly frequent among several risk groups, including older patients, those with hypertension, obesity, cardiovascular, pulmonary and renal diseases, autoimmunity disturbances, and cancer. COVID-19 is associated with severe thrombotic complications, both micro- and macrovascular, substantially including deep vein thrombosis (DVT), pulmonary embolism (PE), primary pulmonary arterial thrombosis, up to disseminate intravascular coagulation (DIC)-like syndrome.<sup>1–4</sup>

Cancer patients are more vulnerable to COVID-19 infection and their disease course is likely to be more aggressive. A recent report evaluated 1,524 patients, admitted to the Department of Radiation and Medical Oncology of Zhongnan Hospital of Wuhan University. While the rate of COVID-19 was 0.79% among cancer patients, it was 0.37% in the general population of Wuhan during the same time period (odds ratio [OR]: 2.31, 95% confidence interval [CI]: 1.89–3.02). Patients with non-small-cell lung cancer (NSCLC) displayed higher incidence of COVID-19, especially those > 60 years of age (4.3 vs. 1.8% in those aged  $\leq$  60 years with NSCLC).<sup>5</sup> In another study from China, cancer patients were found to have higher risk of severe events (i.e., death or admission to the intensive care unit [ICU] for invasive ventilation) (7/18 [39%] vs. 124/1,572 [8%] patients;  $p = 0.0003$ ).<sup>6</sup>

The COVID-19 and Cancer Consortium (CCC19) registry recently reported a large cohort study of 928 patients from the United States, Canada, and Spain. The primary endpoint

was all-cause mortality within 30 days of diagnosis of COVID-19. The median age was 66 years (57–76), and 50% of patients were males. The leading malignancies were breast (21%) and prostate (16%). The ratio of active anticancer treatment or active (measurable) cancer was high, 39 and 43%, respectively. As per analysis dated May 7, 2020, 121 (13%) patients died. The independent risk factors associated with 30-day mortality included age (per 10 years; partially adjusted OR: 1.84, 95% CI: 1.53–2.21), smoking status (1.60, 1.03–2.47), male sex (OR: 1.63, 95% CI: 1.07–2.48), number of comorbidities (2 vs. none: OR: 4.50, 95% CI: 1.33–15.28), the Eastern Cooperative Oncology Group performance status of 2 or higher (OR: 3.89, 95% CI: 2.11–7.18), active cancer (5.20, 2.77–9.77), and use of azithromycin plus hydroxychloroquine (OR: 2.93, 95% CI: 1.79–4.79). Of note, ethnicity, obesity, tumor type, and the anticancer therapy applied had no impact on mortality. As for environmental factors, residence in Canada or the U.S.-Midwest were associated with decreased 30-day all-cause mortality compared with residence in the U.S.-Northeast (OR: 0.24, 95% CI: 0.07–0.84 and OR: 0.50, 95% CI: 0.28–0.90, respectively).<sup>7</sup>

## Thrombosis and Cancer

Venous thromboembolism (VTE) events are common among cancer patients, and their occurrence contributes significantly to morbidity and mortality.<sup>8,9</sup> The risk of VTE is increased by five- to sevenfold among patients with malignant diseases, while fatal PE is three times more common in this population relative to noncancer patients. Annually, 0.5% of cancer patients experience thrombosis compared with a 0.1% incidence rate in general population. Arterial events (i.e., acute myocardial infarctions [MIs] and ischemic strokes) are also more common in cancer patients with solid tumors. In a large retrospective study, including 279,719 pairs of patients with

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cancer and matched controls, the 6-month cumulative incidence of arterial thromboembolism was 4.7% in patients compared with 2.2% in controls.<sup>10</sup> In a recent report on 32,141 hematological cancer patients, the 10-year absolute risk of thrombotic complications following cancer diagnosis was 3.3% for MI, 3.5% for ischemic stroke, and 5.2% for VTE. Overall, patients with hematological cancer were at increased risk for MI, ischemic stroke, and VTE compared with general population.<sup>11</sup> In cancer patients, DIC may present in a chronic form, often exacerbating into a full-blown state following surgery, chemotherapy, infections, etc.<sup>12</sup>

VTE risk assessment in cancer patients is based on the evaluation of patient-related, tumor-related, and treatment-related parameters.<sup>13</sup> Increased age, comorbidities, and prolonged immobility are relatively common among patients with severe COVID-19 disease. Whether the risk of VTE development in active-cancer patients infected with SARS-CoV2 is higher than in COVID-19 patients without malignancies remains to be determined.

## Mechanisms of Thrombosis in Cancer and COVID-19 Patients

The three components of the Virchow's triad are relevant both in cancer and COVID-19 patients. In these diseases, the endothelial wall is damaged, leading to a shift toward a procoagulant phenotype. Stasis of blood is increased due to prolonged hospitalization and immobilization, especially in patients under mechanical ventilation and in those admitted to the ICU. Importantly, proinflammatory cytokines, induced by COVID-19 and cancer, are major contributors to thrombosis development in both clinical scenarios. Indeed, several of these cytokines, reported to be found in patients with SARS-CoV2 infection, are also secreted by tumor and host cells, in the setting of cancer-associated thrombosis (CT).<sup>14</sup> In this context, tumor necrosis factor- $\alpha$  and interleukin (IL)-1 can contribute to thrombus formation by inducing tissue factor (TF) and von Willebrand factor (VWF) expression on vascular endothelial cells, increasing the level of the fibrinolysis inhibitor plasminogen activator inhibitor-1 and attenuating anticoagulant effects via downregulation of thrombomodulin expression.

TF has a crucial role in promoting coagulation and angiogenesis in both solid and hematological malignancies. Pulmonary and peripheral endothelial cell injury due to direct viral attack can activate the coagulation system via exposure of TF and other procoagulant pathways.<sup>15</sup> In a recently published study evaluating patients with COVID-19, endothelial cell involvement across vascular beds of different organs (lung, heart, kidney, liver, and intestine) was demonstrated.<sup>16</sup> In all cases, viral elements were found within endothelial cells and accumulation of inflammatory cells was observed, with evidence of endothelial and inflammatory cell death. Based on these findings the authors suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement and host inflammatory response.

TF is also expressed by mononuclear cells and macrophages in response to proinflammatory cytokines.<sup>17</sup> In severe inflam-

mation, coagulation is mainly dependent on the recruitment of TF-expressing inflammatory monocytes by activated endothelial cells.<sup>18</sup> Other possible contributors to the induction of TF expression and inflammatory programs in monocytes are oxidized phospholipids.<sup>19</sup> These molecules which are produced in oxidative stress, have been found in lungs of patients with severe SARS-CoV (another corona virus).<sup>20</sup>

TF-bearing extracellular vesicles (EVs), released from a variety of cells, including tumor and endothelial cells, are known to be involved in CT.<sup>21</sup> As EVs are reported to play a role in inflammation and thrombosis, they are likely to take part in the thrombotic process revealed in severe COVID-19 infection.

Likewise, cancer-associated neutrophil extracellular traps (NETs), DNA-associated mesh of neutrophil-derived proteases and histones, may facilitate activation of host cells to promote arterial and thrombotic events.<sup>22</sup> For instance, NETs can serve as a platform for direct platelet adhesion and aggregation.<sup>23</sup> Furthermore, NET-associated histones can indirectly augment platelet aggregation by increasing VWF released from activate endothelial cells. Neutrophilia is a prognostic marker in COVID-19 disease and excessive neutrophil infiltrates have been observed in autopsy lung samples of COVID-19 patients. It has been proposed that neutrophilia could also be a source of excess NETs in this setting and that inhibiting NET formation should be a target for therapy in COVID-19.<sup>24</sup>

## Management of Cancer Patients Diagnosed with COVID-19

### VTE Prophylaxis

Recent guidelines emphasize the role of low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) in CT management.<sup>25</sup> It is crucial that the risk for VTE be evaluated in every acutely ill patients with COVID-19, utilizing the available risk-assessment tools (e.g., the Caprini, IMPROVE, and Padua models).<sup>26,27</sup> In general, patients with COVID-19 and active cancer should receive pharmacological VTE prophylaxis, unless there are contraindications. Prophylactic daily LMWHs, or twice-daily subcutaneous unfractionated heparin (UFH) are recommended by the World Health Organization interim guidance statement.<sup>28</sup> It can be argued that due to very high thrombotic risk, patients with active cancer and severe COVID-19 may need intermediate doses of LMWH<sup>29</sup> and that monitoring anti-Xa levels could be of help to optimize anticoagulation.

If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis (intermittent pneumatic compression) should be considered in immobilized patients.<sup>28</sup> The role of thromboprophylaxis for nonhospitalized cancer patients with mild COVID-19 is uncertain. However, in patients with active cancer and limited mobility who are quarantined, the use of pharmacologic prophylaxis should be weighed against the risks of bleeding. The role of extended prophylaxis after hospital discharge has not been studied in COVID-19 patients. Nevertheless, for cancer patients, prolonged use of LMWH prophylaxis for up to 6 weeks with monitoring D-dimer levels

seems reasonable. Although heparin-induced thrombocytopenia (HIT) is uncommon in patients treated with LMWH, fondaparinux could be considered for lowering the risk of HIT in cancer patients with COVID-19.

### VTE Treatment

Therapeutic anticoagulation is the mainstay of VTE treatment in cancer patients with COVID-19. Of note, bleeding risk and renal functions should be taken into consideration. While DOACs are currently increasingly employed in CT,<sup>30</sup> potential drug–drug interactions with investigational anti-COVID-19 drugs should be taken into account. For example, using lopinavir/ritonavir requires dose adjustments of apixaban and betrixaban, while edoxaban and rivaroxaban should not be co-administered with these drugs. Only dabigatran can be safely used with these agents. Tocilizumab, an IL-6 inhibitor, which may be employed for the treatment of COVID-19-induced cytokine storm, increases expression of CYP3A4; however, no dose adjustments are currently recommended with concomitant use of DOACs at this time. The use of azithromycin (a known P-gp inhibitor) with edoxaban or betrixaban also deserves caution, and dose reduction of these factor Xa inhibitors is recommended. Of note, a further analysis of the drug–drug interaction of apixaban in CT is underway. Taken together, nonoral anticoagulation (e.g., UFH or LMWH) is preferred as it can be temporarily withheld and has no known drug–drug interactions with investigational COVID-19 therapies.<sup>31</sup> Additional information about potential drug–drug interaction of oral anticoagulants with anti-COVID-19 drugs is available at <https://www.covid19-druginteractions.org/>.

The treatment of VTE in hematological malignancies is challenging as severe thrombocytopenia is common in hematological patients due to bone marrow infiltration by tumor cells, toxicity of chemotherapy or targeted therapies, etc.<sup>32</sup> Furthermore, in clinical trials of CT, only a minority of patients had hematological malignancies, and usually patients with severe thrombocytopenia were excluded. Recently, a recent guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis on the management of CT patients with thrombocytopenia suggested the following approach.<sup>33</sup> In brief, in thrombocytopenic (i.e., < 50,000/ $\mu$ L) patients with high risk for thrombosis progression or recurrence (symptomatic segmental or more proximal PE, proximal DVT, or a history of recurrent/progressive thrombosis), full-dose anticoagulation in conjunction with platelet transfusion should be administered. For patients with lower risk events a dose-modification strategy using 50% or prophylactic-dose LMWH may be considered. In severe thrombocytopenia (i.e., < 25,000/ $\mu$ L) anticoagulation should be withheld, although prophylactic doses might be reasonable in patients with a platelet count of > 10,000/ $\mu$ L. Inferior vena cava (IVC) filter placement should be considered only in patients with absolute contraindications to anticoagulation. Therefore, retrievable IVC filters may be considered on a case-by-case basis in patients with acute VTE who have severe, prolonged thrombocytopenia or actively bleeding for which anticoagulation with platelet transfusion cannot be achieved.

LMWH is currently the preferred anticoagulant among patients with CT and thrombocytopenia, and DOACs are not recommended.

### Conclusion

Extrapolating the antithrombotic strategy to cancer patients with COVID-19 is challenging due to the paucity of data and the high risk for both thrombosis and bleeding. Rapidly emerging data will hopefully foster management regimens for these critically ill patients.

#### Conflict of Interest

Dr. Brenner reports personal fees from Pfizer, LEO Pharma, Sanofi, ROVI Laboratories, and Bayer Pharmaceuticals, outside the submitted work.

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