



# Thrombosis, cancer, and COVID-19

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Received: 13 October 2021 / Accepted: 28 April 2022 / Published online: 14 May 2022  
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## Abstract

Cancer and coronavirus disease 2019 (COVID-19) have unusual similarities: they both result in a markedly elevated risk of thrombosis, exceptionally high D-dimer levels, and the failure of anticoagulation therapy in some cases. Cancer patients are more vulnerable to COVID-19 infection and have a higher mortality rate. Science has uncovered much about SARS-CoV-2, and made extraordinary and unprecedented progress on the development of various treatment strategies and COVID-19 vaccines. In this review, we discuss known data on cancer-associated thrombosis (CAT), SARS-CoV-2 infection, and COVID-19 vaccines and discuss considerations for managing CAT in patients with COVID-19. Cancer patients should be given priority for COVID-19 vaccination; however, they may demonstrate a weaker immune response to COVID-19 vaccines than the general population. Currently, the Centers for Disease Control and Prevention recommends an additional dose and booster shot of the COVID-19 vaccine after the primary series in patients undergoing active cancer treatment for solid tumors or hematological cancers, recipients of stem cell transplant within the last 2 years, those taking immunosuppressive medications, and those undergoing active treatment with high-dose corticosteroids or other drugs that suppress the immune response. The mainstay of thrombosis treatment in patients with cancer and COVID-19 is anticoagulation therapy.

**Keywords** Cancer · COVID-19 · Thrombosis · COVID-19 vaccines · Anticoagulation

## Introduction

Coagulopathy and disorders of hemostasis are commonly associated with both cancer and coronavirus disease 2019 (COVID-19) infection; thus, cancer patients with COVID-19 have an accumulative risk for thrombosis. Cancer-associated thrombosis (CAT) and COVID-19 have unusual similarities: both result in a markedly elevated thrombosis risk, including

multi-system thrombosis, exceptionally high D-dimer levels, and the failure of anticoagulation therapy in some cases [1, 2] (Table 1). CAT and COVID-19 are associated with high morbidity and mortality rates.

COVID-19 is an infectious pandemic disease that is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA  $\beta$ -coronavirus with a lipidic envelope, and four types of proteins involved in its pathogenicity [3]. SARS-CoV-2 infection was first described in Wuhan, China, in December 2019 [4]. While approximately 80% of people infected with SARS-CoV-2 have a mild disease course, the remaining 20% progress to more severe illness. The overall mortality rate of COVID-19 is 2–3% [5]; it has resulted in millions of deaths worldwide. In addition, some COVID-19 patients develop severe complications, including systemic inflammatory response syndrome, acute respiratory disease syndrome, multiple-organ failure, and shock. These presentations are prevalent among several risk groups, including older patients and those with hypertension; obesity; cardiovascular, pulmonary, or renal disease; autoimmune disorders; or cancer [6]. The leading cause of death from COVID-19 is acute respiratory distress syndrome.

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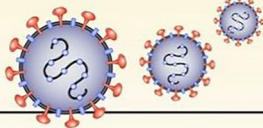
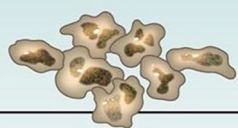
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**Table 1** COVID-19 versus cancer: compared and contrasted concerning D-dimers, thrombus formation, and failure of anticoagulation

	 <b>COVID-19</b>	 <b>CANCER</b>
<b>Mechanism of generation of D-dimers</b>	<ul style="list-style-type: none"> <li>• Thrombi breakdown</li> <li>• Intra-alveolar fibrinolysis driven by SARS-CoV-2-induced thromboinflammation</li> </ul>	<ul style="list-style-type: none"> <li>• Thrombi breakdown</li> <li>• Extravascular fibrinolysis in the malignant stroma, driven by the neoplastic process</li> </ul>
<b>Site of initial thrombus formation</b>	<ul style="list-style-type: none"> <li>• Pulmonary vasculature</li> </ul>	<ul style="list-style-type: none"> <li>• Adjacent to the lesion site in solid tumors</li> </ul>
<b>Local versus systemic thrombosis</b>	<ul style="list-style-type: none"> <li>• Initiates as pulmonary thrombi</li> <li>• In severe cases, thrombosis in multiple vascular beds</li> </ul>	<ul style="list-style-type: none"> <li>• Differentiation not easy</li> <li>• DVT, PE, unusual-site venous thrombi or arterial thrombi</li> </ul>
<b>Triggers for thrombi</b>	<ul style="list-style-type: none"> <li>• Thromboinflammation/immunothrombosis</li> <li>• Endotheliitis</li> <li>• Stasis from immobility</li> </ul>	<ul style="list-style-type: none"> <li>• Cancer procoagulant</li> <li>• Vascular damage: tumor-related and treatment-related</li> <li>• Stasis from compression or immobility</li> </ul>
<b>Rationale for anticoagulant failure</b>	<ul style="list-style-type: none"> <li>• Multiple mechanisms: inflammation, platelet hyperactivity, complement and contact system activation, and others</li> </ul>	<ul style="list-style-type: none"> <li>• Multiple mechanisms: cancer progression, platelet activation, immune activation, and others</li> </ul>

DVT deep vein thrombosis, PE pulmonary embolism

In this article, we discuss known data on thrombotic events associated with cancer, SARS-CoV-2 infection, and COVID-19 vaccines and discuss considerations for managing CAT in patients with COVID-19.

## Cancer and thrombosis

The potential mechanisms of cancer-related hypercoagulability include stasis (direct pressure on blood vessels by the tumor mass), poor performance status, and bed rest following surgical procedures; iatrogenesis as a result of antineoplastic treatment; and secretion of heparinase from malignant tumors that results in the degradation of endogenous heparin [7].

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is serious and potentially life-threatening. VTE may be a harbinger of an occult malignancy or represent a complication of a known malignancy; it can complicate hospitalization, surgery, or various systemic cancer treatments [8].

Cancer patients have a two- to 20-fold higher risk of developing VTE compared to non-cancer patients; of all cases of VTE, 20% occur in cancer patients [9]. Annually, 0.5% of cancer patients experience thrombosis, compared to 0.1% of the general population.

VTE is associated with higher morbidity and mortality rates in cancer patients. It represents the second leading cause of death in hospitalized patients with cancer, the primary cause of death in ambulatory patients undergoing chemotherapy, and the second most common cause of early postoperative mortality; fatal PEs are three times more common in this population than in non-cancer patients [8–12]. VTE is also associated with decreased survival compared to that in patients without VTE. VTE may interrupt needed cancer treatments and increase the risk of bleeding, as the use of anticoagulants may result in significant hemorrhagic complications [8, 13]. Furthermore, the economic burden of VTE in patients with cancer is substantial, as VTE increases healthcare expenditures [9]. Lyman et al. estimated the average cost per hospitalization, adjusted to 2015 US dollars, as \$19,994 in patients without VTE and \$37,352 in patients with VTE [14]. In addition, one-fourth of patients with cancer and VTE undergo readmission as a result of bleeding or a recurrent VTE [15]. Cancer patients with VTE report increased psychological burden and distress [16].

Arterial events (i.e., acute myocardial infarctions and ischemic strokes) are more common in cancer patients with solid tumors and hematologic malignancies than in non-cancer patients [3]. For instance, in a large retrospective study of 748,662 Medicare beneficiaries, the risk of arterial thromboembolic events was 69% higher in the year before cancer diagnosis; this increased risk started 5 months before

the cancer was officially diagnosed, peaking in the month prior [17]. Moreover, among 32,141 hematologic cancer patients, the 10-year absolute risks of thrombotic complications following cancer diagnosis were 3.3% for myocardial infarction, 3.5% for ischemic stroke, and 5.2% for VTE; all of these rates were higher than those in the general population [18].

Disseminated intravascular coagulation (DIC) may present in a chronic form in cancer patients but is often exacerbated into a more phenotypically aggressive expression following surgery, chemotherapy, or infection [19].

## Coagulopathy in COVID-19

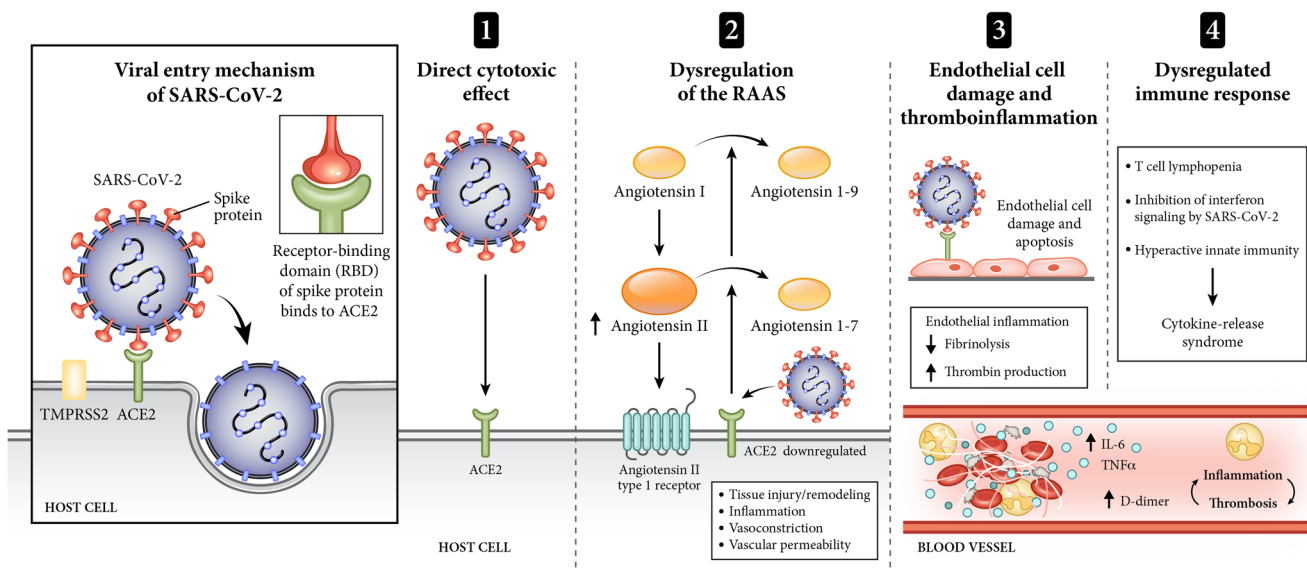
Coagulopathy in COVID-19 has several proposed pathophysiologic mechanisms that initiate when the viral particles are inhaled into the respiratory system through aerosol droplets and invade alveolar lung cells by selectively binding the SARS-CoV-2 spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on the surface of airway epithelial cells [20] (Fig. 1). The S protein is primed by the cellular serine protease TMPRSS2 or other proteases; co-expression on the cell surface of ACE2 and TMPRSS2 is required to complete the entry process.

Cellular heparan sulfate is a proposed co-receptor for SARS-CoV-2 binding to ACE2; exogenous heparin may affect viral adhesion [21].

COVID-19-associated prothrombosis results from increased coagulation, decreased fibrinolysis, and immune effects. VTE has been found in up to 50% of COVID-19 autopsy series, with possible embolic complications and in situ microvascular immunothrombosis. Immunothrombosis, including innate immune cell activation, excessive coagulation, and endothelial dysfunction, has been proposed as an essential pathological prothrombotic mechanism in patients with COVID-19 [22].

The initial binding of SARS-CoV-2 to type II pneumocytes within the alveoli results in mass infiltration of immune cells, including monocytes, macrophages, and neutrophils, and contributes to a hypercoagulable state and hyperinflammation, which is caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), and tumor necrosis factor (TNF)- $\alpha$  [22, 23].

Severe COVID-19 is characterized by increased activation of the immune system and heightened inflammation and is associated with an amplified and uncontrolled release of cytokines, a phenomenon that has been termed cytokine storm [24]. The hyperinflammatory response triggered by



**Fig. 1** Pathophysiology of coagulopathy in COVID-19. SARS-CoV-2 enters host cells by interacting its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (left). The proposed mechanisms for COVID-19 associated coagulopathy include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS due to downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II. ACE2 cleaves angiotensin II (AngII) to angiotensin 1-7 (Ang1-7). Invasion of the endothelial cells by SARS-CoV-2 causes internalization of the ACE2 receptor, promoting an imbalance of Ang1-7 and AngII,

in favor of the latter, resulting in suppression of Ang1-7-mediated vasodilation and accumulation of AngII, which binds to angiotensin II receptor type 1 (AT1), with potential to exacerbate pulmonary vasoconstriction and induction of tissue factor (TF) and plasminogen activator inhibitor 1 (PAI-1) expression on platelets and the endothelium; (3) endothelial cell damage and immunothrombosis or thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNF $\alpha$ .

SARS-CoV-2 is a significant cause of disease severity and death.

Another proposed mechanism of hypercoagulability in COVID-19 is through complement activation, an essential inducer of coagulation [22]. The complement component C5a may contribute to the recruitment of neutrophils. Neutrophils can release web-like structures that are composed of DNA filaments coated with histones and granule proteins; these structures are known as neutrophil extracellular traps (NETs) [25]. The generation of NETs as a defense mechanism by neutrophils is another process that promotes coagulation, and NETs may facilitate the activation of host cells to promote arterial and thrombotic events. Histones, a significant component of NETs, attract and bind platelets, resulting in their adhesion and aggregation [25]. Furthermore, NET-associated histones can enhance platelet aggregation indirectly through the increased release of the Von Willebrand factor from activated endothelial cells. A low neutrophil count is a prognostic marker in COVID-19 disease; an abundance of neutrophil infiltrates has been seen in lung samples of autopsies of COVID-19 patients [26]. In this setting, neutrophilia could be a source of excess NETs and impeding NET formation could be targeted in COVID-19 therapy [27] (Fig. 2).

Endothelial damage is present in COVID-19, caused directly by viral invasion and indirectly by inflammation and resulting in disruption of the intercellular junction, with exposure to the subendothelial matrix that contains tissue factor (TF) and collagen and leading to activation of the coagulation cascade via the extrinsic pathway. Exposure of TF and collagen results in thrombin formation and the conversion of fibrinogen to fibrin, which, along with platelet aggregates, forms blood clots. Mild prolongation of the prothrombin time in COVID-19-associated coagulopathy may represent activation of the TF extrinsic pathway. Inflammatory cytokines can induce TF expression on macrophages and platelets in COVID-19; furthermore, inflammation in COVID-19 could impair the TF pathway inhibitor (TFPI), leading to further coagulation. COVID-19 is also

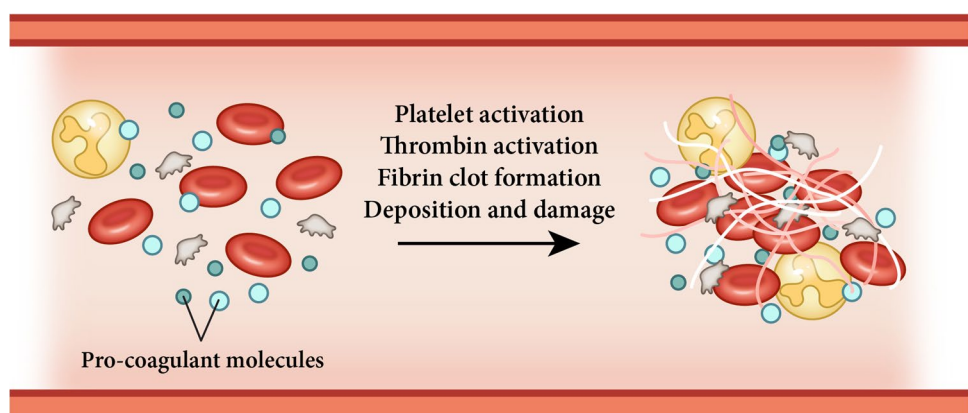
associated with increased markers of endothelial activation (Von Willebrand factor, FVIII, and P-selectin), and elevated levels of soluble thrombomodulin (an endothelial glycoprotein), together with Von Willebrand factor, are associated with worse clinical outcomes. Simultaneous with endothelial dysfunction and activation of the extrinsic pathway by COVID-19, platelets are recruited and activated to the site of endothelial injury, further contributing to hypercoagulability [28].

Severe COVID-19 is associated with reduced fibrinolysis, and increased VTE has been observed in patients with significant clot dissolution abnormalities. The paradoxical combination of high levels of D-dimer (a marker of fibrinolysis), increased levels of the fibrinolytic inhibitor plasminogen activator inhibitor 1 (PAI-1), and evidence of apparent hypofibrinolysis may be a consequence of the differences between systemic and local effects or may be caused by the fibrinolytic system being overwhelmed by the failed attempt to remove fibrin and necrotic tissue from the lung parenchyma [29]. Levels of the fibrinolytic inhibitor plasminogen activator inhibitor 1 are increased in COVID-19, SARS-CoV-1 infection, and other causes of acute respiratory distress syndrome in which hypofibrinolysis and fibrin deposition are hallmarks [22].

Local hypoxia exacerbates prothrombosis by inducing P-selectin, TF, and Von Willebrand factor expression on the endothelial surface. Hypoxia activates the cyclooxygenase pathway, releasing thromboxanes A<sub>2</sub> and B<sub>2</sub>, resulting in vasoconstriction [30]. Vascular tone is also regulated by hypoxia-independent mechanisms, including the renin–angiotensin–aldosterone system. Viral entry downregulates ACE2, leading to reduced cleavage of angiotensin I and angiotensin II (AngII). The accumulated AngII binds to the angiotensin II receptor type 1, potentially exacerbating pulmonary vasoconstriction and inducing TF and PAI-1 expression on platelets and the endothelium [31].

Additional mechanisms that are associated with thrombosis in COVID-19 are increased ferritin levels, which likely reflect cellular damage that may contribute to inflammation

**Fig. 2** Neutrophil Extracellular Traps (NETs)



[32], and elevated antiphospholipid antibody titers, which have been described in COVID-19 but whose significance is unclear [33].

Patients with COVID-19 may have mild thrombocytopenia, mildly prolonged prothrombin time, increased fibrinogen, and raised D-dimer levels, all of which are more pronounced as the disease severity increases [34, 35]. COVID-19-associated coagulopathy shares features with sepsis-induced coagulopathy and disseminated intravascular coagulation but is a distinct entity [36].

SARS-CoV-2 binds to the ACE2 receptors that are widely expressed on endothelial cells in multiple organs. SARS-CoV-2 has been detected in the kidneys, liver, heart, and brain, accounting for the extrapulmonary thrombotic complications observed in COVID-19 [23]. Varga et al. demonstrated endothelial cell involvement across vascular beds of different organs (lungs, heart, kidneys, liver, and intestine) in a series of patients with COVID-19. Viral elements were found in endothelial cells in all cases, with evidence of endothelial and inflammatory cell death. On the basis of these findings, the authors suggested that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement and host inflammatory response [37]. The clinical outcomes of COVID-19 are worse in patients with diseases that are associated with endothelial dysfunction (e.g., systemic hypertension, diabetes, and obesity), and evidence of endothelial dysfunction was found in a COVID-19 autopsy series [38].

### Clinical implications of thrombosis in cancer and COVID-19

The three components of the Virchow's triad are relevant to cancer and COVID-19 patients [39]. Damage to the endothelial walls is found in both conditions and leads to hypercoagulability. Blood stasis increases as a result of prolonged hospitalization and immobilization, especially in patients undergoing mechanical ventilation; the average length of ICU stay for patients with severe COVID-19 infection is 12.4 to 18.9 days [40, 41]. Moreover, proinflammatory cytokines, induced by COVID-19 and cancer, contribute significantly to the development of thrombosis in both conditions. Various cytokines reported in patients with SARS-CoV-2 infection are also produced by tumor and host cells in the setting of CAT [42].

TF plays a vital role in promoting coagulation and angiogenesis in solid tumors and hematological malignancies. Pulmonary and peripheral endothelial cell injury as a result of direct viral attack can activate the coagulation system via exposure of TF and other procoagulant pathways [43].

TF-bearing extracellular vesicles are released from various cells, including tumor and endothelial cells, and are

known to be involved in CAT [44]. As extracellular vesicles are reported to play a role in inflammation and thrombosis, they are likely to participate in the thrombotic process in severe COVID-19 infections.

### Thrombosis risk stratification of cancer patients with COVID-19

Cancer patients are more vulnerable to infection by SARS-CoV-2, and patients with hematological malignancies, lung cancer, or metastatic disease have the highest incidence of severe events [45], as are recipients of stem cell transplants and adoptive cellular therapies [46–48].

In an analysis of the Lean European Open Survey on SARS-CoV-2 Infected Patients (LEOSS) registry of 435 cancer patients and 2636 non-cancer patients with confirmed SARS-CoV-2 infection, male sex, advanced age, and active malignancy were associated with higher death rates. After adjusting for other risk factors, the mortality was comparable. At detection of SARS-CoV-2, 62.5% presented with mild symptoms, 55% progressed to severe COVID-19, and 27.5% were admitted to the ICU. The COVID-19-related mortality rate was 22.5%. Despite comparable outcomes after adjusting for age, sex, and comorbidities, these results emphasize that cancer patients as a group are at higher risk for adverse outcomes as a result of their advanced age and pre-existing conditions [49].

The COVID-19 and Cancer Consortium (CCC19) registry cohort study [50] collected de-identified data on 928 patients, aged 18 years and older, from the USA, Canada, and Spain with an active or previous malignancy and a confirmed COVID-19 infection. Their median age was 66 years (range, 57–76 years), and 50% were male. The most common cancers were breast (21%) and prostate (16%). The 30-day all-cause mortality rate in these patients was high. The independent risk factors that were associated with 30-day mortality included age (increasing per 10 years; partially adjusted OR: 1.84, 95% CI: 1.53–2.21), smoking status (OR: 1.60, 95% CI: 1.03–2.47), male gender (OR: 1.63, 95% CI: 1.07–2.48), number of comorbidities (2 versus 0: OR: 4.50, 95% CI: 1.33–15.28), Eastern Cooperative Oncology Group performance status of 2 or higher (OR: 3.89, 95% CI: 2.11–7.18), active malignancy (OR: 5.20, 95% CI: 2.77–9.77), and use of azithromycin plus hydroxychloroquine (OR: 2.93, 95% CI: 1.79–4.79). Other factors, such as ethnicity, obesity, type of tumor, and anticancer treatment, had no effect on mortality [50].

The risk of VTE in patients with both cancer and COVID-19 remains mostly unknown; no studies have found an association as a result of sample size limitations. Nopp et al. conducted a systematic literature search to identify all studies that reported VTE rates in patients

with COVID-19. Eighty-six studies were identified, and 66 (28,173 patients) were included in the quantitative analysis. ICU admissions occurred in 19.4% of cases; of these, 10.1% were cancer patients (805 of 7979), and 3.6% with active cancer (55 of 1509). VTE occurred in 14.1% of patients overall (95% CI, 11.6–16.9%), 8.6% of cancer patients (95% CI, 0.72–1.88%;  $p = 0.42$ ), and 22.7% of ICU patients (95% CI, 18.1–27.6%). However, the VTE risk was also higher in non-hospitalized patients. Patients who developed VTE had higher D-dimer levels. A higher proportion of men than women had severe disease, a difference that only increased among patients admitted to the ICU, suggesting that men are more likely to experience severe disease than women. Correspondingly, men were at higher risk of developing VTE, but no association was observed between comorbidities and VTE risk, including age and cancer, suggesting that the high VTE baseline risk of COVID-19 overwhelms other risk factors [51].

The COVID-19 and Cancer Consortium (CCC19) cohort of 1629 hospitalized cancer patients with COVID-19 concluded that recent anticancer therapy, active cancer, high-risk VTE cancer subtypes, and ICU admission were associated with an increased risk of VTE and PE. In contrast, pre-admission anticoagulant or antiplatelet therapy may reduce the risk [52].

## COVID-19 vaccines and thrombosis

The rapid spread of SARS-CoV-2 has elicited an equally rapid response: safe and effective vaccines against COVID-19 have been developed as the best approach to controlling and ultimately ending the pandemic. SARS-CoV-2 has a characteristic S protein that induces humoral and cellular immune responses against SARS-CoV-2, making it a potent target for vaccine development [53]. Given their vulnerability, cancer patients should be given priority for vaccination [54].

To date, no specific safety concerns have been identified for COVID-19 vaccines in patients with cancer. However, most COVID-19 vaccine phase 3 studies excluded these patients [54]. Considering the high mortality risk associated with SARS-CoV-2 infection in patients with cancer, the effectiveness of COVID-19 vaccines at preventing severe infection in the general population, and the low incidence of significant adverse effects, several professional oncological societies and other health care organizations have established that the risk–benefit ratio favors vaccinating cancer patients [55].

Patients with cancer may experience a weaker immune response to COVID-19 vaccines than the general population. In the UK SOAP-02 study of 95 patients with solid tumors, 56 patients with hematologic malignancies, and

54 healthy controls, anti-S protein immunoglobulin levels measured 21 days after the first BNT162b2 (Pfizer-BioNTech COVID-19) vaccine dose revealed adequate levels of immune protection in 97% (31 of 32) of controls, 39% (21 of 54) of patients with solid tumors, and 13% (5 of 39) of patients with hematologic malignancies. Some of the serological non-responders demonstrated increased numbers of T cells secreting IFN- $\gamma$  or IL-2. Remarkably, 95% (18 of 19) patients with solid tumors who received the booster dose at day 21 showed protective levels of anti-SARS-CoV-2 antibodies at week 5 [56].

The Centers for Disease Control and Prevention recommends that an additional primary vaccine dose be given at least 28 days after the second dose of BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) or mRNA-1273 (Moderna COVID-19 vaccine) and a booster dose given 5 months after completing the primary series in people who are moderately to severely immunocompromised, including patients undergoing active cancer treatment for solid tumors or hematologic cancer, recipients of stem cell transplants within the last 2 years, those taking immunosuppressive medications, and those undergoing active treatment with high-dose corticosteroids or other drugs that suppress the immune response (e.g., cancer patients undergoing treatment for immune-related adverse events with immune checkpoint inhibitors [ICIs]). Among immunocompromised patients who received the Janssen's Ad.26.COV2.S vaccine, no additional primary shot is recommended at this time, with a booster at 2 months with either BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) or mRNA-1273 (Moderna COVID-19 vaccine) after the first shot [57].

In theory, COVID-19 vaccines could affect the toxicity or efficacy of ICIs [58]. Nonetheless, the safety data available so far are encouraging, with no evidence of increased immune-related adverse events. In an Israeli study, 134 patients with cancer undergoing ongoing ICI therapy received two doses of the BNT162b2 vaccine. The most common local adverse events were injection site pain (63%) and local swelling (9%), whereas the most common systemic side effects were muscle pain (34%), fatigue (34%), and headache (16%), followed by fever, chills, and gastrointestinal complications (10% each). This toxicity profile was comparable between the ICI-treated cancer patients and a matched cohort of healthy controls; no vaccine- or ICI-related severe adverse events were observed [58].

The current SARS-CoV-2 variants of concern include B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.617.2 (delta), and B.1.1.529 (omicron), which were first identified in the UK, South Africa, Brazil, India, and South Africa, respectively. These strains may differ with respect to transmissibility, lethality, and response to vaccines.

Thrombosis associated with thrombocytopenia (known as thrombosis with thrombocytopenia syndrome,

vaccine-induced immune thrombotic thrombocytopenia, or vaccine-induced prothrombotic immune thrombocytopenia) is a rare syndrome that has been reported in individuals, especially younger women, who received AstraZeneca's post-adenoviral-based COVID-19 ChAdOx1 nCoV-19 vaccine, a recombinant chimpanzee adenoviral vector that encodes the S protein [59], or Janssen's Ad.26.COV2.S vaccine, a recombinant human adenovirus type 26 vector that encodes the S protein [60]. Thrombosis with thrombocytopenia syndrome often has a cerebral or abdominal location and is associated with platelet-activating antibodies against platelet factor 4. The use of heparin should be avoided in these patients unless HIT is negative. Various regulatory agencies have advised caution with adenoviral-based COVID-19 vaccines in people at higher risk of blood clots because of underlying medical conditions, regardless of age [61]. This guidance could affect patients with cancer, considering that malignancy itself is associated with an increased risk of thromboembolism. However, it is currently believed that the benefits of these vaccines outweigh the risks in most people.

### Thromboprophylaxis and thrombosis treatment in cancer patients with COVID-19

Patients with active cancer and COVID-19 should undergo pharmacological VTE prophylaxis unless contraindications are present. These patients may also require intermediate doses of low-molecular weight heparin [62] because of their very high thrombosis risk and because anti-Xa level monitoring could help optimize anticoagulation. Mechanical VTE prophylaxis (intermittent pneumatic compression) should be considered in immobilized patients who have contraindications for pharmacological prophylaxis. The role of thromboprophylaxis in non-hospitalized cancer patients with COVID-19 is uncertain.

Therapeutic anticoagulation is the mainstay of VTE treatment in cancer patients with COVID-19. Factors such as bleeding risk, renal and hepatic function, and potential drug-drug interactions should be considered when selecting therapeutic agents.

Direct oral anticoagulants are increasingly used to treat CAT [63, 64]. However, potential drug-drug interactions should be considered with investigational anti-COVID-19 drugs. For instance, tocilizumab, an IL-6 inhibitor that may be employed to treat COVID-19-induced cytokine storms, increases the expression of CYP3A4; nonetheless, no dose adjustments are recommended for concomitant use of direct oral anticoagulants.

The treatment of VTE in patients with hematologic malignancies is challenging: these patients may present with severe thrombocytopenia as a result of bone marrow

infiltration by tumor cells and chemotherapy or targeted therapy toxicities. Furthermore, clinical trials of CAT treatments have only included a minority of patients with hematologic malignancies, excluding those with severe thrombocytopenia. The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommendations on treating CAT patients with thrombocytopenia should be followed [65]. Placement of an inferior vena cava filter should only be reserved for patients with absolute contraindications to anticoagulation. Retrievable inferior vena cava filters may be considered on a case-by-case basis in patients with acute VTE who have severe, prolonged thrombocytopenia or active bleeding for which anticoagulation with platelet transfusion cannot be achieved. The currently preferred anticoagulant among patients with CAT and thrombocytopenia is low-molecular weight heparin, and direct oral anticoagulants are not recommended.

### Conclusions

Cancer patients are at increased risk for VTE, including deep-vein thrombosis and PE, and arterial thromboembolic events. Similarly, COVID-19 infection is associated with coagulopathy and hemostasis disorders. Cancer patients infected with SARS-CoV-2 may have a cumulatively higher risk of thrombosis.

The mechanisms that contribute to increased thrombosis in COVID-19 entail an extensive interaction between hemostasis and the immune system, and treatments that target these pathways may mitigate the adverse macrovascular and microvascular effects of COVID-19.

The coagulopathy features of cancer patients with acute COVID-19 illness differ from the classic findings seen in disseminated intravascular coagulation; increased levels of fibrin degradation products (D-dimer) and average platelet counts, followed by increased consumption of platelets, seem to be common in severe and fatal illnesses.

On the basis of available data and first-hand experience, cancer patients seem to be more vulnerable to infection by SARS-CoV-2, and patients with hematologic malignancies, lung cancer, or metastatic disease have the highest rate of severe events, as well as the recipients of stem cell transplants and adoptive cellular therapies. However, it is unclear whether cancer patients with COVID-19 are at increased risk of VTE, as VTE rates vary across different health care settings (ICU versus non-ICU, hospitalized versus ambulatory patients, university versus community settings, and urban versus rural) and thromboprophylactic strategies.

Cancer patients should be vaccinated against SARS-CoV-2, given the high efficacy of these vaccines in preventing severe infection in the general population and the low incidence of severe adverse effects. The Centers for Disease

Control and Prevention is currently recommending an additional dose and a booster shot of the COVID-19 vaccine after completing the primary series to people who are moderate to severely immunocompromised, including patients undergoing active cancer treatment for solid tumors or hematologic cancers, recipients of stem cell transplants within the last 2 years, those taking immunosuppressive medications, and those undergoing active treatment with high-dose corticosteroids or other drugs that suppress the immune response. The mainstay of treatment for CAT with COVID-19 is anticoagulation therapy.

**Acknowledgements** We thank the following individuals for their expertise and assistance with editing and medical illustrations:

Ann Sutton  
Editing Services, Research Medical Library  
The University of Texas MD Anderson Cancer Center  
Angela Diehl  
Scientific and Medical Illustration

**Author contribution** Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals.

**Data availability** The manuscript has associated data and is in a data repository.

**Code availability** Not applicable.

## Declarations

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare no competing interests.

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