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# COVID-19 associated coagulopathy and thrombosis in cancer

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ABSTRACT

Cancer patients are at risk for a more severe COVID-19 infection as well as an adverse outcome of such infection. This may be caused by the cancer itself (e.g haematological malignancies and lung cancer) or due to immune suppression caused by anti-cancer treatment. Severe COVID-19 infections are often complicated by a coagulopathy that clinically results in a high incidence of venous thromboembolic disease. Cancer itself is associated with a hypercoagulable state and a markedly increased incidence of thromboembolic complications, hence the combination of cancer and COVID-19 may amplify this risk. COVID-19 vaccination seems safe and effective in most cancer patients although adapted and bespoke vaccination schemes may increase the seroconversion rate and immune response in selected patients. Specific management strategies to improve outcomes of cancer patients in COVID-19 (e.g. higher intensity antithrombotic prophylaxis) are lacking and should be evaluated in clinical studies simultaneously focusing on efficacy and safety.

## 1. Introduction

Severe COVID-19 caused by SARS-CoV-2 is associated with significant morbidity, including respiratory insufficiency and multiple organ dysfunction, and relatively high mortality. The more severe infections were initially considered as a form of community-acquired pneumonia, often evolving into more widespread acute lung injury and acute respiratory distress syndrome (ARDS). However, it became quickly apparent that apart from the lungs multiple other organs could be compromised and therefore the concept that COVID-19 is a viral sepsis with an ensuing systemic inflammatory syndrome affecting the entire body became widely accepted [1].

Risk factors for more severe COVID-19 as well as an adverse outcome are among others age, obesity, and pre-existent comorbidities such as diabetes, uncontrolled hypertension, and pulmonary disease. In addition, patients with a compromised immune system, such as patients after organ transplant, haematological disease and those receiving immunosuppressive or anti-neoplastic agents, are at very high risk for more severe COVID-19 [2].

Patients with serious manifestations of COVID-19 display hemostatic abnormalities that are strong predictors of respiratory deterioration and mortality [3,4]. Moreover, many of those patients develop venous thromboembolism [5]. There is solid evidence that pulmonary embolism contributes to a sudden decline of pulmonary oxygen exchange which is frequently seen in critically ill COVID-19 patients. This is all very relevant to cancer patients that indeed may have an impaired immune response due to the disease and/or the medication that is used to manage the malignancy. In addition, the pre-existent risk of thromboembolic complications in cancer patients is already 12-fold increased [6].

In this review we will briefly describe the pathogenetic pathways involved in COVID-19 coagulopathy and thereafter focus on the significance of COVID-19 for cancer patients in terms of outcome, the risk of thromboembolic complications and management consequences.

## 2. COVID-19 coagulopathy

Coagulation changes in COVID-19 are somewhat similar to other sepsis-related forms of deranged coagulation (in its most severe form presenting as disseminated intravascular coagulation (DIC)) [7]. However, some features are distinct from sepsis-associated hemostatic changes, so that it is usually referred to as “COVID-19-associated coagulopathy” [8]. COVID-19-associated coagulopathy is typically associated with highly elevated D-dimer levels, which are strong predictors for

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a more severe clinical course and an adverse outcome as well as for venous thromboembolism. Of note, D-dimer levels can also be increased in patients with cancer but the D-dimer elevation is frequently more profound in patients with severe COVID-19. Other characteristics are elevated plasma concentrations of fibrinogen and factor VIII, likely as a result of the acute phase response driven by pro-inflammatory cytokines, notably interleukin (IL)-6 [9]. Many patients have a mild thrombocytopenia (100-150 $\times$ $10^9$/l) whereas more reduced platelet counts are rarely (<5%) seen [10]. However, thrombocytopenia is a marker for a higher risk of severe disease. A meta-analysis indicated that a drop in platelet count of 30 $\times$ $10^9$/l in COVID-19 patients or thrombocytopenia below the lower limit of normal was associated with a more than five-fold higher risk of severe disease [11]. Plasma levels of physiological coagulation inhibitors such as antithrombin and protein C can be mildly decreased, in particular in non-surviving patients, but these concentrations rarely decline below 80% of normal [4,12]. Several studies have reported abnormal overall clotting and increased viscoelastic parameters by thrombelastography [13]. Overt DIC is infrequently seen in COVID-19 infection except for some critically ill patients with multi-organ failure [14].

Apart from the cytokine-induced and tissue factor-mediated activation of the coagulation cascade that is common in severe infections and a systemic inflammatory state, COVID-19 infections have other distinct effects on the coagulation system. Coronavirus infections are associated with a typical fibrinolytic profile. Experiments in mice with a targeted deletion of the urokinase-type plasminogen activator (u-PA) gene pointed to a urokinase-driven route as an important factor in mortality [15]. Also, in human SARS-CoV-1 infection plasma levels of tissue-type plasminogen activator (t-PA) were 6-fold higher than normal [16]. It may be hypothesized that the marked release of plasminogen activators from the endothelium plays a role in the high levels of D-dimer that is seen in severe COVID-19. One can speculate that the resulting plasmin activates metalloproteinases that are involved in extracellular matrix modification required for capillary leakage and lung edema.

Another important contributor to COVID-19 associated coagulopathy is the formation of neutrophil extracellular traps, which are web-like structures composed of DNA, histones, and proteins released from the nucleus of hyperactived, dying neutrophils. Inducers of NET formation include IL-8 and complement activation, both of which are key aspects of COVID-19 [17]. These intravascular NETs promote thrombus formation by triggering activation of the intrinsic coagulation pathway and by providing a scaffold for platelets, red blood cells, and procoagulant molecules such as von Willebrand factor. Markers for NETosis, such as myeloperoxidase-DNA complex and citrullinated histone H3, appear to be higher in patients with COVID-19 than in controls, but are also higher in patients with severe COVID-19 than in those with mild COVID-19, suggesting a role for NETs in mediating disease severity. For example, it was shown that citrullinated histone H3 positive neutrophils (indicative of neutrophils displaying NET formation) colocalize with platelets within microthrombi present in the lungs of patients with COVID-19-related acute respiratory distress syndrome [18]. NETs were also abundant in coronary thrombi of patients who developed myocardial infarction in relation to COVID-19, while atherosclerotic plaques were absent. Together, these findings demonstrate that NETosis is common in patients with COVID-19 and may be one of the drivers of COVID-19 coagulopathy.

There is evidence for a specific endothelial cell involvement in COVID-19. Although SARS-CoV-2 (and other coronaviruses) were considered to be able to directly infect endothelial cells [19], this rather unique feature was recently questioned by others [20]. Nonetheless, endothelial cell perturbation and injury will provide a perfect surface for intravascular thrombus formation. It may also may cause augmented platelet-vessel wall interaction, as a result of the massive release of high molecular weight von Willebrand factor multimers from injured endothelium, which will overwhelm the cleaving capacity of ADAMTS13, and cause thrombotic microangiopathy in the microvasculature of various organs [21,22].

## 3. Relevance of COVID-19 coagulopathy

COVID-19 associated coagulopathy causes a hypercoagulable state that results in an enhanced risk of thromboembolic complications. Immobilisation, indwelling lines in hospitalized patients and vascular damage further increase the risk of thrombosis. A pooled analysis of clinical observational studies in more than 2000 patients suggested an incidence of venous thrombosis and pulmonary embolism in about 30% in patients with severe COVID-19 [23,24]. A meta-analysis estimated the incidence of venous thromboembolism at 18% of hospitalized COVID-19 patients, growing to 28% in patients admitted to critical care units [25]. Some retrospective studies indicated an even higher risk of venous thromboembolism in those with more severe COVID-19 coagulopathy. There is quite some variation between the reported incidences in individual studies which probably can be ascribed to including non-symptomatic diagnoses (obtained by systematic screening) in the cohorts and variable use of antithrombotic prophylaxis. The relevance of (microvascular) thrombosis for organ dysfunction has also been suggested based on post-mortem pathological reports. Several reports demonstrated vascular changes, including wall thickening, vessel stenosis, and microthrombi formation associated with multiple organ failure and acute lung injury [26].

## 4. Cancer and COVID-19

Already early in the pandemic it became clear that cancer patients, in particular those who had recent chemotherapy or major surgery, were at high risk for more severe COVID-19 and an adverse outcome [27,28]. Several registries confirmed the higher risk of cancer patients. For example, the OnCOVID study collected data from 890 European patients with cancer and COVID-19 and reported a mortality of 34% [29,30]. Other cohorts confirmed this finding and identified patients with haematological disease and lung cancer at particularly high risk [31,32].

A large cohort study of 928 patients with cancer and COVID-19 demonstrated that independent factors associated with increased 30-day mortality included advanced age (per 10 years odds ratio: 1.8), male sex (odds ratio: 1.6), smoking status (odds ratio former smoker versus never smoked: 1.6), Eastern Cooperative Oncology Group performance status of 2 or higher (odds ratio status of 2 versus 0 or 1: 3.9), and active cancer (odds ratio progressive cancer versus remission: 5.2) [33].

A meta-analysis of 15 studies encompassing more than 3000 patients found a case-fatality rate of COVID-19 in cancer patients of 25% [34]. Age and male sex were independent risk factors of a poor prognosis in the infected cancer patients. Similarly, in another systematic review of 52 studies including more than 18.000 cancer patients the COVID-19 related mortality was 25% [35]. In a pooled analysis of 28 studies involving 1276 patients with COVID-19 that were admitted to a critical care unit mortality was 60%. The odds ratio for death in cancer patients compared to non-cancer patients was 1.9 (95% confidentiality interval 1.6–2.3). In particular patients with haematological malignancies had an almost two-fold higher mortality than patients with other forms of cancer [36]. This finding underscores the importance of the malignancy itself affecting the immune response, immune suppression by chemotherapy, and treatment related cardiovascular, pulmonary and renal toxicity of anti-neoplastic treatment.

A cohort of almost 400.000 adult patients with cancer were selected out of 4.3 million patients populating the National COVID Cohort Collaborative (N3C) and 16% of these patients had COVID-19 [37]. The presence of COVID-19 was associated with a 1.2-fold increased risk of death in cancer patients with age, comorbidity, haematological cancer, multi-tumor sites and recent anti-cancer treatment as independent risk factors for overall mortality. Interestingly, immunotherapy or non-cytotoxic targeted treatment was not associated with a poor prognosis.

## 5. COVID-19 associated coagulopathy and thrombosis in cancer patients

Precise estimates of the risk of coagulopathy and venous thromboembolism in patients with cancer are scarce and data from prospective studies are lacking.

Small observational studies suggest that the inflammatory and coagulation response to a COVID-19 infection in cancer patients is larger than in non-cancer patients [38]. In a retrospective survey of 1244 COVID-19 patients, 140 cancer patients were compared with a1,104 non-cancer patients [39]. Patients with cancer had increased levels of leukocyte and neutrophil count whereas the lymphocyte count was significantly lower. Plasma levels of D-dimer were markedly higher in the cancer group, in particular in those with severe COVID-19.

There is somewhat more information on the thrombotic risk of cancer patients with COVID-19. A retrospective study compared 2779 patients with COVID-19 complicated by venous thromboembolism in 16 centers in China with 23,000 non-COVID-19 medical inpatients. Overall, mild and severe COVID-19 increased the risk of developing symptomatic venous thrombosis and pulmonary embolism by a factor 3 and 6, respectively [40]. In this study active cancer was the most prominent risk factor for developing thrombosis in patients with COVID-19. In a study in 2804 hospitalized COVID-19 patients with cancer the incidence of venous thromboembolism was higher (10%) in patients receiving recent anti-cancer therapy than in those without treatment (6%). Other risk factors for venous thromboembolism in cancer and COVID-19 were cancers with a known high risk of thrombosis (such as pancreatic or gastric cancer), previous thrombosis, ICU triage on admission, ethnicity, and significant D-dimer elevation [41]. There are also some reports of smaller studies suggesting that the thrombotic risk associated with COVID-19 is not additive to the risk of thrombosis in cancer patients. One study in 45 cancer patients with COVID-19, calculated an incidence of 14% of thrombosis in the cancer group compared with 18% in a non-cancer control group. However cancer patients were more often on therapeutic dose anticoagulants than controls in this study. Of note survival was significantly shorter in the group with active cancer compared to non-cancer patients [42].

## 6. Consequences for the management of patients with cancer and COVID-19

COVID-19 is a major threat for patients with active cancer, in particular during immune-modulating treatment or after major surgery. Hence, optimal protection of these patients against a COVID-19 infection is of paramount importance. Vaccination provides adequate protection against severe disease also in cancer patients and although protection conferred by conventional vaccination schemes may be insufficient, tailored vaccination strategies can often overcome this obstacle (see next paragraph).

There is a strong case for optimal thrombosis prophylaxis in cancer patients with COVID-19 in view of their dual and possibly additive risk to develop venous thromboembolism. However, higher intensity antithrombotic regimes may carry the risk of hemorrhagic complications, which is also higher in cancer patients compared to non-cancer patients. So far, no randomized controlled trials on the optimal dose intensity of antithrombotic prophylaxis specifically aimed at cancer patients have been reported.

In general, there is an urge to increase the dose of thromboprophylaxis to therapeutic-dose anticoagulation, or a dosing intensity between conventional prophylaxis and therapeutic levels ('intermediate dose'). A recent cohort study of more than 1300 adults hospitalized with COVID-19 indicated that receiving any dose of anticoagulation (versus no anticoagulation) was associated with a significantly lower in-hospital mortality; however, only prophylactic-dose anticoagulation was associated with lower mortality at 60 days [43].

There are several trials evaluating anticoagulant prophylaxis against venous thromboemboism in COVID-19 (Table 1). The ATTACC, ACTIV-4a and REMAP-CAP investigators evaluated the efficacy and safety of therapeutic-dose anticoagulation in an open-label adaptive multiplatform RCT [44,45]. They found no benefit on a primary outcome of organ support-free days and death and a higher bleeding risk in patients on the intensive care unit but a better outcome (and only slightly more bleeding) in hospitalized non-intensive care patients. In the recent RAPID trial therapeutic dose low molecular weight heparin did not significantly lower the composite risk of death, invasive mechanical ventilation, or admission to the intensive care unit (primary outcome) in hospitalized COVID-19 patients, but was associated with a significantly lower chance of death (1.8% versus 7.6%; odds ratio 0.22) [46]. The INSPIRATION trial randomized severe COVID-19 patients to either intermediate-dose (1 mg/kg enoxaparin daily) or standard-dose (40 mg enoxaparin daily) thromboprophylaxis in critically ill patients with COVID-19 [47]. Among the 562 patients included in the primary analysis, there was no significant difference between the two groups. Similarly, full dose rivaroxaban was not associated with better outcomes than standard-dose heparin in patients hospitalized with COVID-19 and elevated D-dimer concentrations [48].

Taken together, whereas there is increasing evidence that higher intensity thrombosis prophylaxis is somewhat more effective and only slightly less safe compared to conventional dose prophylaxis in hospitalized patients with COVID-19, clinical studies do not support higher doses of antithrombotic prophylaxis in more severely ill patients, mostly because of an enhanced risk of bleeding in more severely ill patients. One could argue this finding could be extrapolated to cancer patients who also have an increased bleeding risk.

Another topic that has not yet been addressed is antithrombotic prophylaxis in non-hospitalized cancer patients who develop COVID-19.

**Table 1**
Summary table of randomized controlled trials comparing different intensities of thrombosis prophylaxis in patients with COVID-19.

| Trial | Patients | Result |
|---|---|---|
| ATTACC/ ACTIV4a/ REMAP-CAP [45] | Intensive Care Unit patients with COVID-19 | No benefit of higher intensity heparin prophylaxis on primary outcome of organ support-free days and death and increased bleeding risk |
| ATTACC/ ACTIV4a/ REMAP-CAP [44] | Hospitalized non-Intensive Care Unit patients with COVID-19 | Better outcome on primary outcome of organ support-free days and death in higher intensity heparin prophylaxis group despite slightly increased bleeding risk |
| RAPID [46] | Hospitalized COVID-19 patients | No effect of higher intensity thrombosis prophylaxis on primary outcome of composite risk of death/invasive mechanical ventilation/ICU admission but better survival (secondary outcome) in high intensity group |
| INSPIRATION [47] | Severe COVID-19 patients | No difference between intermediate dose and standard dose thrombosis prophylaxis |
| ACTION [48] | Hospitalized COVID-19 patients | No difference between therapeutic oral rivaroxaban and standard thrombosis prophylaxis |
| HEP-COVID [56] | Hospitalized COVID-19 patients with high D-dimer levels or high sepsis-induced coagulopathy score | Reduction of composite risk of major thromboembolism and death in therapeutic heparin group versus prophylactic/ intermediate dose heparin group |
| ACTIV-4b [49] | Outpatients with COVID-19 | No difference between prophylactic-dose apixaban, therapeutic-dose apixaban, aspirin and placebo |

For non-cancer patients this is currently not advised awaiting ongoing clinical trials. The recent ACTIV-4b randomized controlled trial compared prophylactic-dose apixaban, therapeutic-dose apixaban, aspirin, placebo in clinically stable outpatients with COVID-19 [49]. There was no difference in outcomes between the four arms, although the study was largely underpowered as it was terminated early after enrolment of 657 because of a lower-than-anticipated event rate. However, the risk benefit balance for cancer patients may tip in favour of (conventional dose) thrombosis prophylaxis for outpatients during an active COVID-19 infection but this needs confirmation in appropriate clinical studies.

## 7. COVID-19 vaccination and cancer

The expedited registration phase III trials for the anti-COVID-19 vaccines included only 0.4–2% of patients with active cancer [50]. Nevertheless all vaccines are considered safe for cancer patients despite theoretical concerns of enhanced permeation and retention of mRNA in cancer cells for the mRNA vaccines and the risk of adenoviral vectors (albeit non-replicative) for the alternative vaccines. Obviously, when considering the risks of vaccination against COVID-19 in cancer patients, one should also take into account the risk of delayed or suboptimal cancer management due to avoidance of medical care and hospitals by unvaccinated subjects.

A systematic review compared vaccine efficacy in 621 cancer patients reported in 6 publications with 256 controls [51]. The authors found similar seroconversion rates but lower antibody titres in cancer patients. Of note, patients with haematological malignancies had significantly lower rates of seroconversion.

A recent prospective study in 500 patients with solid tumors and 240 control subjects who were vaccinated with the Moderna mRNA-1273 SARS-CoV-2 vaccine showed no significant difference between the two groups (97 to 99% seroconversion) regardless of concurrent treatment with anti-cancer treatment or immunotherapy [52]. Antibody titres were somewhat lower in the cancer patients, in particular those on active anti-cancer treatment, but the relevance of this towards protection against severe COVID-19 is not clear.

In those patients that do not respond well to COVID-19 vaccination there is now an alternative as SARS-CoV-2 neutralising monoclonal antibodies have become available [53]. The monoclonal antibody sotrovimab was shown to lower the risk of COVID-19 progression in high-risk patients with mild-to-moderate Covid-19 [54]. REGEN-COV decreased the risk of Covid-19-related hospitalization or death in outpatients at high risk of severe COPVID-19 infection and attenuated symptoms more rapidly than placebo [55]. However, although this treatment was shown to be safe, there is not yet convincing evidence that it provides a meaningful improvement in clinically relevant outcomes. Studies specifically aimed at cancer patients with or without anti-cancer treatment have not yet been performed.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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