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Review

Thromboembolic Disease in Patients With Cancer and COVID-19: Risk Factors, Prevention and Practical Thromboprophylaxis Recommendations–State-of-the-Art

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Abstract. *Cancer and COVID-19 are both well-established risk factors predisposing to thrombosis. Both disease entities are correlated with increased incidence of venous thrombotic events through multifaceted pathogenic mechanisms involving the interaction of cancer cells or SARS-CoV2 on the one hand and the coagulation system and endothelial cells on the other hand. Thromboprophylaxis is recommended for hospitalized patients with active cancer and high-risk outpatients with cancer receiving anticancer treatment. Universal thromboprophylaxis with a high prophylactic dose of low molecular weight heparins (LMWH) or therapeutic dose in select patients, is currently*

indicated for hospitalized patients with COVID-19. Also, prophylactic anticoagulation is recommended for outpatients with COVID-19 at high risk for thrombosis or disease worsening. However, whether there is an additive risk of thrombosis when a patient with cancer is infected with SARS-CoV2 remains unclear. In the current review, we summarize and critically discuss the literature regarding the epidemiology of thrombotic events in patients with cancer and concomitant COVID-19, the thrombotic risk assessment, and the recommendations on thromboprophylaxis for this subgroup of patients. Current data do not support an additive thrombotic risk for patients with cancer and COVID-19. Of note, patients with cancer have less access to intensive care unit care, a setting associated with high thrombotic risk. Based on current evidence, patients with cancer and COVID-19 should be assessed with well-established risk assessment models for medically ill patients and receive thromboprophylaxis, preferentially with LMWH, according to existing recommendations. Prospective trials on well-characterized populations do not exist.

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global health crisis with catastrophic social and economic impact that has been unparalleled in the last 100 years (1). COVID-19 is a systemic disease that implicates activation of endothelial cell and blood hypercoagulability and its manifestations vary from asymptomatic to severe respiratory dysfunction and multi-organ failure (1). Early in the pandemic, it was observed that COVID-19 is associated with abnormal coagulation parameters coupled with the occurrence of both arterial and venous thromboembolic events, and also with potential bleeding manifestations in certain patients (2, 3). Regarding venous thromboembolic events (VTEs), many epidemiological studies report a high incidence in patients with COVID-19 (4-6), and, additionally, it has been demonstrated that early prophylactic anticoagulation is associated with improved clinical outcome and with some survival benefit (7-9). Therefore, it is recommended that hospitalized patients with COVID-19 and outpatients with COVID-19 at high risk of VTE or high risk of disease worsening receive prophylactic anticoagulation; the dose and duration of thromboprophylaxis though vary according to different guidelines (10). It should be noted that each patient carries an individual risk factor for thrombosis. The degree of COVID-19 severity together with the individual's physical condition and comorbidities determine the total risk of disease worsening and thrombosis (10).

Patients with cancer and COVID-19 are a particularly vulnerable subgroup since they might be immunocompromised due to anticancer therapy or cancer itself, or due to old age with other underlying comorbidities (11). It has been shown that 30-day all-cause mortality is high for patients with COVID-19 and cancer (11, 12) and these patients have an increased case-fatality rate compared to patients without cancer (13). It is well-established that cancer carries an intrinsic risk for thrombosis, which is heterogeneous across different malignancies (14). Intriguingly, the similarities between cancer and COVID-19 regarding their pro-thrombotic effect have been highlighted (15); however, whether there is an additive effect in the risk of thromboembolic events when a patient with cancer is infected with SARS-CoV-2 remains unclear (16). Hence, there are no particular recommendations for prophylactic anticoagulation in patients with cancer and COVID-19 in inpatient or outpatient settings (10). Given the ongoing pandemic, it is helpful to identify any distinct characteristics and requirements of each subgroup of patients to deliver the appropriate antithrombotic treatment. In this context, the aim of this review was to summarize and critically discuss the current evidence on thrombotic risk and prophylactic anticoagulation strategies in patients with cancer and COVID-19.

COVID-19 and Thrombosis

Epidemiology. COVID-19 is associated with a pattern of hypercoagulability coupled with a high incidence of thrombotic phenomena (2). A large body of epidemiological studies has established a strong association between severe COVID-19 with an increased VTE risk, including pulmonary embolism (PE) and deep vein thrombosis (DVT) (17-21). In a meta-analysis of 102 studies with follow-up duration that ranged from 8 to 86 days, the overall prevalence rates of PE and DVT among patients with COVID-19 were 7.8% and 11.2%, respectively, with statistically significant higher prevalence in the series that systematically screened patients compared to series of symptomatic patients (22). The rate of patients receiving pharmacological thromboprophylaxis among the included studies of this meta-analysis ranged from 16% to 100% (22). The incidence of VTEs is associated with the severity of COVID-19, with the highest risk observed in critically ill patients in the intensive care unit (ICU) (19, 23). The manifestation of VTE is associated with about 2-fold increased mortality. Interestingly, in situ thrombosis in small pulmonary vessels (termed "pulmonary intravascular coagulation") seems relevant in COVID-19, as revealed from several autopsy studies of patients whose cause of death was COVID-19 (24). SARS-CoV-2 infection might also be associated with an increased prevalence of arterial thrombotic events such as ischemic stroke, systemic arterial embolism, mesenteric ischemia and limb ischemia, which occur in approximately 4% of critically ill COVID-19 patients (25). Hemorrhage may occur in patients with severe COVID-19, indicating a COVID-19-related endothelium damage effect though its incidence is significantly lower as compared to thrombosis, particularly regarding clinically relevant, major bleeding events (17, 26).

Pathogenesis. Several mechanisms have been proposed in order to explain the hypercoagulability of COVID-19. All of them can be assessed by applying the principles of Virchow's triad, *i.e.*, the three pillars for thrombogenesis: (a) blood stasis, (b) endothelial injury, and (c) hypercoagulability (27). Hospitalized and, especially, critically ill patients are in prolonged immobility, thus they exhibit blood stasis. It is well known that SARS-CoV-2 infects host cells *via* binding to angiotensin-converting enzyme-2 (ACE2) and facilitated by transmembrane protease serine type 2 (TMPRSS2) in S protein priming (28, 29). ACE2 is abundantly expressed in a variety of cells in different tissues, mainly in lung alveolar epithelial cells, cardiac myocytes, and vascular endothelium (30). Endothelial cells account for one-third of the overall cellular population of the lungs. The direct invasion of the virus leads to endothelial cell injury, which disrupts the antithrombotic functions of endothelial cells (31-33). Initial evidence of endothelial injury comes from the elevated von Willebrand factor (VWF) levels, a glycoprotein synthesized by megakaryocytes and endothelial cells, which initiates platelet adhesion as a response to endothelial damage (34, 35). Accumulating evidence have documented that endothelial cell activation is a constituent process upon SARS-CoV-2 infection and COVID-19 (36). Accordingly, biomarkers of endothelial cell activation, *e.g.*, soluble thrombomoduline, free tissue factor pathway inhibitor (TFPI) and tissue factor (TF) activity in plasma are prognostic risk factors for intubation and death (37). Biomarkers of hypercoagulability and particularly increased levels of D-Dimers are predictors of disease worsening and mortality (38). Finally, activated neutrophils and their ability to release extracellular chromatin and form neutrophils extracellular traps (NETs), induce thrombus formation and appear to be potentially implicated in COVID-19 thrombosis (39).

Thrombotic risk assessment. Patients with COVID-19 are considered as a high VTE risk population *per se*. However, individual thrombotic risk stratification is highly recommended, and is valuable in daily clinical practice in order to initiate prophylaxis interventions and monitor patients throughout the disease. In this context, already established and validated risk assessment models (RAMs) for acutely ill hospitalized medical patients, namely the Padua Prediction Score (PPS), the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE-RAM), and the Geneva Risk Score (40), are currently utilized and recommended for patients with COVID-19 particularly at the outpatient setting (41, 42). Also, a modified version of IMPROVE incorporating D-dimers, the IMPROVE-DD model, has been externally validated in patients with COVID-19 (43, 44). The risk assessment of disease worsening is also important when managing patients with COVID-19. To this end, COMPASS-COVID-19 has been developed in order to identify patients with COVID-19 at risk of clinical deterioration and remains to be externally validated (45).

Thromboprophylaxis recommendations. Given the high thrombotic risk in patients with COVID-19, thrombo-prophylaxis strategies were early initiated in hospitalized patients with COVID-19 and associated with a survival benefit (7, 8). Therefore, universal prophylactic thromboprophylaxis, chiefly with the use of low molecular weight heparin (LMWH), is currently recommended for hospitalized patients with COVID-19 in all national and international guidelines (10, 46, 47). Defining the optimal dose for high-risk inpatients with COVID-19, with the use of higher-than-usual prophylactic doses has been investigated (48). Evidence from randomized control trials (RCTs) now supports the use of therapeutic-dose LMWH in select ward (non-ICU) COVID-19 inpatients (49-51), which are endorsed by international antithrombotic guidelines (46, 47). Regarding outpatients, guidelines recommend non-pharmacological measures for all COVID-19 patients, such as adequate mobility and hydration, and pharmacological interventions in patients with high VTE and low bleeding risk as well as in patients at high risk of disease worsening (47). A recent 4-arm RCT in COVID-19 outpatients did not show benefit of the direct oral anticoagulant (DOAC) apixaban or aspirin, although the trial was underpowered, and the results of two other trials with LMWH and the DOAC rivaroxaban are pending (52, 53). It is suggested that post-discharge patients are prescribed prolonged thromboprophylaxis up to 45 days in the case of high VTE risk (10). A recent RCT investigating the use of thrombo-prophylaxis in the post-discharge setting showed that rivaroxaban 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis (54).

Cancer-associated Thrombosis

Epidemiology. In 1865, French physician Armand Trousseau, after the irony of self-diagnosis, reported migratory thrombophlebitis as a complication of cancer, from which he died two years later, in 1867 (55). Since then, various studies have revealed the correlation between thrombosis and cancer. Thrombotic events that occur in the setting of malignancy are referred to as cancer-associated thrombosis (CAT). CAT constitutes the second leading cause of mortality among cancer patients (14).

The devastating thromboembolic events in malignancy can affect the venous and arterial systems. Venous thromboembolic events, including DVT and PE, are more common and well-studied thrombotic manifestations in cancer patients than arterial thrombotic events (ATE) (56). It is estimated that cancer patients have a 5-to-7-fold increased risk of developing VTE (57), and approximately 20% of all VTE cases are

attributed to malignancy (58). The estimated annual incidence of VTE in cancer patients is 0.5% compared with 0.1% in the general population and is associated with shortened survival (57, 59). Notably, unprovoked VTE can be the first manifestation of a previous undiagnosed tumor (60). Regarding ATE, a recent study with data derived from the Surveillance, Epidemiology and End Results (SEER) database demonstrated that cancer patients have a 2-fold increased risk for ATEs (61).

Pathogenesis. The aberrant hemostasis of malignancy has a complex pathogenesis and involves several interactions of tumor cells with the clotting system. Drivers of CAT pathogenesis are the production of procoagulant substances, increased systemic inflammation, and tumor-induced platelet aggregation.

Tissue factor (TF) is a key player of the hypercoagulable state of malignancy. TF is an integral glycoprotein with a high affinity for factor VII/VIIa and, under normal conditions, is separated from the blood by the vascular endothelium (62). In the case of vascular injury or induced expression by endothelial cells, TF becomes exposed to blood and binds FVII/FVIIa. The complex TF/FVIIa enables the initiation of thrombin generation *via* the proteolytic activation of factors IX and X (63). TF is highly expressed in many types of cancer (pancreatic adenocarcinoma, glioma, ovarian cancer), leading to the initiation of the extrinsic coagulation pathway (64). Fibrin clot formation also plays a role in tumor metastasis by protecting circulating cancer cells from shear stress and natural killer cell-mediated attack (64). Other factors derived from cancer cells and contributing to CAT pathogenesis include extracellular vesicles, which are small membrane-enclosed structures that may express TF and phosphatidylserine in their surface and carry procoagulant potential (65-67), and cancer procoagulant (CP), a cysteine protease that directly activates factor X (57). Inflammatory cytokines, such as tumor necrosis factor-a, interleukin-1, and vascular endothelial growth factor, induce the production of TF, decrease the expression of the anticoagulant thrombomodulin (57) and podoplanin, and promote the proliferation of megakaryocytes and formation of platelets (68-71). Also, it has been demonstrated that cancers, through a systemic effect, can induce an increase in peripheral blood neutrophils and promote the formation of NETs which are then released into the extracellular space (72). NETs show pro-coagulant/pro-thrombotic characteristics by serving as scaffolds for blood cells' aggregations or with interactions with other molecules (72).

Thrombotic risk assessment. Thrombotic risk is highly heterogeneous among patients with cancer, as cancer is a heterogeneous disease itself. Each cancer type carries a differential intrinsic risk for thrombosis. Pancreatic and gastric cancers are associated with the highest thrombotic risk, followed by lung, testicular, gynecologic, bladder and central nervous system cancers, which are also frequently complicated with VTE (73). However, prostate cancer, breast cancer, and melanoma are less commonly associated with VTE (58). Advanced stage of cancer is associated with increased risk for VTE as compared to localized stage (14). The time since cancer diagnosis as well as the type of the anticancer treatment are major determinants of the risk of cancer associated thrombosis (74).

Apart from cancer-related risk factors, patient-related and therapy-related risk factors predisposing to CAT have been identified. More specifically, patient-related factors include age (≥65 years), female sex, black race, comorbid conditions (obesity, heart or respiratory disease, renal failure, acute infection, cardiovascular risk factors or disease), immobility, and previous history of VTE (75). Therapy-related factors include major surgery (76), central venous catheters (77), and differential risk associated with chemotherapy agents, where the highest risk is associated with cisplatin, L-asparaginase thalidomide, lenalidomide and tamoxifen (78). An increased risk for ATE has been linked to the use of angiogenesis inhibitors (bevacizumab, aflibercept) and several anti-angiogenic tyrosine-kinase inhibitors (sorafenib, sunitinib, pazopanib) or bcr-abl tyrosine kinase inhibitors (nilotinib, ponatinib) (79).

Several biomarkers have been extensively investigated as potentially predictive of VTE risk. Complete blood count, being practical and ubiquitously available in clinical practice, has been widely studied to predict VTE. In prospective studies of cancer patients, both elevated leukocyte and platelet counts, and low hemoglobin levels were associated with increased risk of initial VTE. Other biomarkers include D-dimers, tissue factor, and novel markers such NETs, procoagulant phospholipid dependent clotting time, and thrombin generation assay as well as genetic polymorphisms (80).

Risk stratification models based on clinical characteristics and biomarkers have been developed to assess VTE risk in cancer. The Khorana score is the most well-known and can be easily applied to patients with active cancer before the initiation of anticancer treatment (81). However, it has a low accuracy in the evaluation of the risk for VTE particularly in patients with cancer associated with moderate or low risk (*i.e.*, lung cancer, breast cancer, prostate cancer, gynecological and colon cancer as well as in lymphoma) and it is not applicable after anticancer treatment initiation (82). The COMPASS-CAT score has been independently validated and is accurate for the prediction of VTE in patients with breast, lung colon or ovarian cancer (83). Other scoring systems, such as VIENNA CATS, PROTECT, and CONKO have been proposed for the evaluation of the risk of CAT in ambulatory patients receiving anticancer therapy (82-87).

Thromboprophylaxis recommendations. According to international guidelines, patients with active cancer should be offered pharmacological thromboprophylaxis in the case

of hospitalization or when they are undergoing cancer surgery. At the outpatient setting, cancer patients receiving anticancer therapy who are at high risk of VTE should receive pharmacological thromboprophylaxis. More specifically, it is suggested that the individual VTE risk of each patient should be assessed with relevant risk stratification models and administration of prophylactic anticoagulation should be considered in high-risk ambulatory patients (88). Parenteral anticoagulants are recommended as first line thromboprophylaxis. DOACs and particularly the specific direct inhibitors of factor Xa (apixaban, betrixaban, edoxaban and rivaroxaban) are becoming promising alternatives to LMWH in the prevention of CAT (89-91).

Thrombosis in Patients With Cancer and COVID-19

Despite the abundance of epidemiological studies on VTE risk in patients with COVID-19 and even though active cancer has been reported as an independent risk factor for symptomatic VTE in patients hospitalized due to COVID-19 (92), there is scarce data from cohorts designed to include specifically this particular subgroup of patients.

In one of the first studies on the incidence of thrombosis and bleeding events in patients with cancer who were hospitalized due to COVID-19, the cumulative incidence of thrombotic events was 18.2% at day 28 in the non-cancer cohort and 14.2% in the cancer cohort. The cumulative incidence of major bleedings at day 28 was 20.8% in the non-cancer group and 19.5% in the cancer cohort. Therefore, the results did not indicate any difference in thrombotic or bleeding risk for patients with cancer (93). Similarly, in a French cohort, it was demonstrated that patients with and without active cancer who were hospitalized due to COVID-19 shared similar outcomes in terms of death, admission in intensive care, or thrombosis/bleeding (94). More specifically, symptomatic DVT occurred in 1.6% of patients with active cancer compared to 1.0% of patients without cancer, and symptomatic PE was diagnosed in 3.2% *versus* 8.5%, respectively (94). No significant differences related to a cumulative incidence of thrombosis between cancer and non-cancer groups were detected (9.8% *vs*. 5.80%) in another study from Spain. Thus, the authors conclude that the thrombotic effect of COVID-19 is not as evident in patients with cancer and does not appear to add to the pro-thrombotic activity of cancer (95).

In another prospective study of patients with non-hematological malignancies and COVID-19, the cumulative incidence of VTE (both symptomatic and asymptomatic) on day 14 after admission was estimated at 10%, without new VTE events after hospital discharge and up to 90 days follow-up; however, the study did not include a control group (96). In another cohort of 90 patients with COVID-19 and active cancer diagnosis, 11 (12.2%) patients were found to have 13 new thromboembolic events within 30 days of COVID-19 diagnosis: 8 (8.9%) arterial and 5 (5.6%) venous (97). In this study, other factors related to cancer, such as cancer type, presence of metastases, and administration of prior chemotherapy, did not correlate with an increased incidence of thromboembolic events (97).

Li *et al*. performed a large cohort study of hospitalized patients with cancer and COVID-19, and the incidence of VTE and ATE was 7.6% and 3.9%, respectively. The frequency of VTE, but not ATE, was higher in patients who had received recent anticancer therapy (98). Interestingly, a simplified risk assessment model for VTE was suggested in the same study and was named CoVID-TE. The parameters included were the following: 1) Cancer subtype high to very-high risk by original Khorana score +1 point, 2) VTE history +2, 3) ICU admission +2, 4) D-dimer elevation +1, 5) recent systemic anticancer Therapy +1, 6) and non-Hispanic ethnicity +1 (98). The RAM stratified the patients of the study into two cohorts (low-risk, 0–2 points, n=1423 *vs*. high-risk, 3+ points, n=1034), and VTE occurred in 4.1% low-risk and 11.3% high-risk patients. When the patients with anticoagulant use prior to COVID-19 diagnosis were excluded, the CoVID-TE RAM demonstrated similarly good discrimination for VTE prediction. However, CoVID-TE RAM has not been externally validated yet (98).

Discussion

Our literature review demonstrated that current data do not support a pro-thrombotic summative effect between cancer and COVID-19, contrary to what one would expect based on the thrombotic pathophysiology of both disease entities. It has been suggested that the overwhelming thrombo-inflammatory state of active COVID-19 may outweigh a more modest hypercoagulable state of active cancer (93). Another explanation might be that patients with cancer, who are generally at risk for severe COVID-19, might be already in a critical situation when the COVID-19 cytokine storm occurs, and therefore, they are likely to die without developing thrombosis (99). Of note, it should be taken into consideration that, mainly during the first pandemic waves, patients with cancer might not had equivalent access to ICU, a setting which is associated with increased risk of thrombosis (100). Interestingly, a recent study defining prognostic factors in patients with COVID-19 and thoracic malignancies did not identify coagulation-related factors as determinants of worse prognosis (101). Finally, it should be noted that the thrombotic and bleeding risks are heterogeneous across cancer sites, stages, or treatment and that the published cohorts, which in general include any cancer history, might not permit the estimation of the risk in a well-characterized population of patients with pro-thrombotic cancer types.

The European Society for Medical Oncology (ESMO) published, at the beginning of the pandemic, consensus

recommendations on the management of patients with cancer and COVID-19 and recommended the use of pharmacological prophylaxis using LMWH or DOACs. It is recommended that prophylaxis of thromboembolic events for patients with cancer should be continued according to existing guidelines (102).

In the absence of specific recommendations for patients with active cancer and COVID-19, first of all, risk assessment approaches may be applied as for non-cancer patients with COVID-19. It is of paramount importance that all guidelines for COVID-19 thromboprophylaxis emphasize the role of thrombotic and bleeding risk stratification before any therapeutic intervention occurs (10). In this context, patients, particularly at the outpatient setting should be assessed with RAMs developed for acutely ill medical patients and recommended for patients with COVID-19, such as the Padua Prediction Score, Geneva Risk Score, and IMPROVE-RAM or IMPROVE-DD. Importantly, all RAMs mentioned above include active cancer as a risk factor for thrombosis, therefore, stratifying the patient with active cancer and COVID-19 at a higher risk *per se*. The introduction of RAMs specific for patients with cancer and COVID-19, as the CoVID-TE could be of some interest as clinical decision support tool as soon as it will be externally validated (98). Considering the assessment of the bleeding risk, the majority of guidelines for COVID-19 thromboprophylaxis incorporate the identification of risk factors (such as low platelet count, history of bleeding events), rather than the usage of risk scoring systems (10). Additional assessment of risk for disease worsening should be applied with pertinent scores (45).

After VTE and disease worsening risk assessments and taking into consideration the existing guidelines for thromboprophylaxis for patients with COVID-19, but in the absence of randomized clinical trials for patients with both active cancer and COVID-19 at the time being, it is reasonable to suggest that these patients could be offered (a) universal high prophylactic-dose LMWH in the setting of hospitalization, with select patients offered therapeutic-dose if they exhibit low bleeding risk, normal renal function, and high risk features, such as a D-dimers >2x upper limit of normal or with oxygen requirements of 2 liters/minute nasal cannula O2 or greater, (b) a prophylactic dose of LMWH in outpatients and at post-discharge up to 45 days. Recently, rivaroxaban at 10mg QD was also associated with clinical benefit at the post-discharge setting; however, the population of the trial did not include patients with active cancer (54).

Evaluation of renal function, bleeding risk, weight, age and caution for potential occurrence of heparin-induced thrombocytopenia (HIT) should be underlined and are of major importance for the improvement of the benefit-risk ratio of thromboprophylaxis (10, 103). Regarding the use of DOACs, even though their prophylactic role for cancer-associated thrombosis is emerging, when it comes to guidelines for COVID-19, most recommendations advise switching to LMWH when a patient is admitted to the hospital is already treated with DOACs (10). At the post-discharge setting though, which means that the patient undergoes the end of the course of COVID-19 infection, thromboprophylaxis with DOACs could be considered as for other patients with active cancer, with special attention to bleeding risk assessment and potential drug-drug interactions. Mechanical measures of thromboprophylaxis (*e.g.*, graduated compression stockings or intermittent pneumatic compression) are also recommended in case of high bleeding risk and contraindication to pharmacological thromboprophylaxis (10).

A proposed algorithm for thromboprophylaxis management of patients with active cancer and COVID-19 is presented in Figure 1.

Conclusion

In conclusion, both cancer and COVID-19 are associated with increased incidence of thromboembolic events; however, an additive thrombotic risk for patients with cancer and COVID-19 has not been proven so far. Therefore, general guidelines for thromboprophylaxis in patients with COVID-19 should be applied, taking into consideration the specialties of the population of patients with cancer regarding their comorbidities and physical condition. Risk stratification for thrombotic and bleeding risk is of utmost importance. The use of well-established RAMs for acutely ill medical inpatients is recommended, and the introduction and validation of novel risk assessment models are greatly anticipated. Finally, prospective and randomized clinical trials of well-characterized cancer populations are needed to determine optimal anticoagulation strategies. Periodically updated evidence-based clinical guidelines and algorithms are essential to improve the quality of clinical decisions and maximize the benefit for patients with cancer and COVID-19.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

E.D, G.G, M.C., D.O. A.S., A.F., A.M, L.A, S.S., J.B., G.G., P.M., B.C., J.S., K.S.: design of the study, literature review, writing of the original draft, figure preparation, revision, and final approval; Cancer-Covid-19 Thrombosis Collaborative Group: literature review, data collection and analysis, writing, revision, and final approval.

Cancer-Covid 19 Thrombosis Collaborative Group

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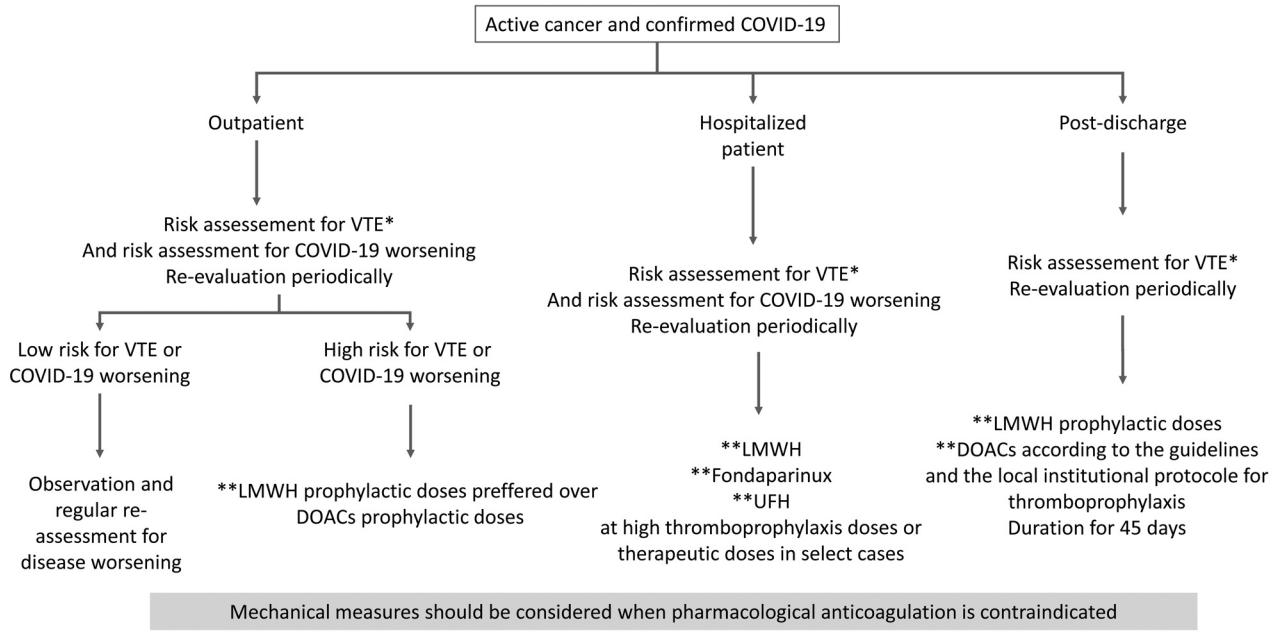

Figure 1. *Suggested algorithm for thromboprophylaxis management of patients with active cancer and COVID-19. VTE: Venous thromboembolism; RAM: risk assessment model; HIT: heparin-induced thrombocytopenia; LMWH: Low molecular weight heparins; DOACs: direct oral anticoagulants; UFH: unfractionated heparin.*

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References

1 Cascella M, Rajnik M, Aleem A, Dulebohn SC and Di Napoli R: Features, evaluation, and treatment of Coronavirus (COVID-19). StatPearls [Internet], 2022. PMID: 32150360.

2 Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ and Rosovsky RP: COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood *136(4)*: 489-500, 2020. PMID: 32492712. DOI: 10.1182/blood.2020006520

3 Tang N, Li D, Wang X and Sun Z: Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost *18(4)*: 844-847, 2020. PMID: 32073213. DOI: 10.1111/jth.14768

4 Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS and Syrigos K: Venous thromboembolism in COVID-19: A systematic review and meta-analysis. Vasc Med *26(4)*: 415-425, 2021. PMID: 33818197. DOI: 10.1177/1358863X21995566

5 Fontelo P, Bastola MM, Zheng Z and Baik SH: A review of thromboembolic events in hospitalized COVID-19 patients. Thromb J *19(1)*: 47, 2021. PMID: 34187490. DOI: 10.1186/s12959-021-00298-3

6 Tufano A, Rendina D, Abate V, Casoria A, Marra A, Buonanno P, Galletti F, Di Minno G, Servillo G and Vargas M: Venous thromboembolism in COVID-19 compared to non-COVID-19 cohorts: a systematic review with meta-analysis. J Clin Med *10(21)*: 4925, 2021. PMID: 34768445. DOI: 10.3390/jcm10214925

7 Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, Skanderson M, Brittain E, King JT Jr, Ho YL, Eden S, Kundu S, Lann MF, Greevy RA Jr, Ho PM, Heidenreich PA, Jacobson DA, Douglas IJ, Tate JP, Evans SJW, Atkins D, Justice AC and Freiberg MS: Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. BMJ *372*: n311, 2021. PMID: 33574135. DOI: 10.1136/bmj.n311

8 Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, Arvind V, Bose S, Charney AW, Chen MD, Cordon-Cardo C, Dunn AS, Farkouh ME, Glicksberg BS, Kia A, Kohli-Seth R, Levin MA, Timsina P, Zhao S, Fayad ZA and Fuster V: Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol *76(16)*: 1815-1826, 2020. PMID: 32860872. DOI: 10.1016/j.jacc.2020.08.041

9 Dimakakos E, Kollias A, Rapti V, Kyriakoulis KG, Trontzas IP, Abdelrasoul MM, Zanelli S, Leontis K, Argyraki K, Dimakou K, Tsoukalas G, Athanasiou K, Nitsotolis T, Syrigos KN and Poulakou G: Early occurrence of adverse events in hospitalized patients with COVID-19 and beneficial effect of anticoagulation. In Vivo *36(1)*: 381-383, 2022. PMID: 34972738. DOI: 10.21873/invivo.12714

10 Kyriakoulis KG, Kollias A, Kyriakoulis IG, Kyprianou IA, Papachrysostomou C, Makaronis P, Kotronias RA, Terentes-Printzios D, Toskas I and Mikhailidis DP: Thromboprophylaxis in patients with COVID-19: Systematic review of National and International Clinical Guidance Reports. Curr Vasc Pharmacol *20(1)*: 96-110, 2022. PMID: 34431465. DOI: 10.2174/1570161119666210824160332

11 Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Hsu CY, Desai A, de Lima Lopes G Jr, Grivas P, Painter CA, Peters S, Thompson MA, Bakouny Z, Batist G, Bekaii-Saab T, Bilen MA, Bouganim N, Larroya MB, Castellano D, Del Prete SA, Doroshow DB, Egan PC, Elkrief A, Farmakiotis D, Flora D, Galsky MD, Glover MJ, Griffiths EA, Gulati AP, Gupta S, Hafez N, Halfdanarson TR, Hawley JE, Hsu E, Kasi A, Khaki AR, Lemmon CA, Lewis C, Logan B, Masters T, McKay RR, Mesa RA, Morgans AK, Mulcahy MF, Panagiotou OA, Peddi P, Pennell NA, Reynolds K, Rosen LR, Rosovsky R, Salazar M,

Schmidt A, Shah SA, Shaya JA, Steinharter J, Stockerl-Goldstein KE, Subbiah S, Vinh DC, Wehbe FH, Weissmann LB, Wu JT, Wulff-Burchfield E, Xie Z, Yeh A, Yu PP, Zhou AY, Zubiri L, Mishra S, Lyman GH, Rini BI, Warner JL and COVID-19 and Cancer Consortium: Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet *395(10241)*: 1907-1918, 2020. PMID: 32473681. DOI: 10.1016/S0140-6736(20)31187-9

12 Desai A, Gupta R, Advani S, Ouellette L, Kuderer NM, Lyman GH and Li A: Mortality in hospitalized patients with cancer and coronavirus disease 2019: A systematic review and meta-analysis of cohort studies. Cancer *127(9)*: 1459-1468, 2021. PMID: 33378122. DOI: 10.1002/cncr.33386

13 Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, Pradhan K, Thota R, Reissman S, Sparano JA, Gartrell BA, Smith RV, Ohri N, Garg M, Racine AD, Kalnicki S, Perez-Soler R, Halmos B and Verma A: Case fatality rate of cancer patients with COVID-19 in a New York Hospital system. Cancer Discov *10(7)*: 935-941, 2020. PMID: 32357994. DOI: 10.1158/2159-8290.CD-20-0516

14 Noble S and Pasi J: Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer *102(Suppl 1)*: S2-S9, 2010. PMID: 20386546. DOI: 10.1038/sj.bjc.6605599

15 Thachil J, Khorana A and Carrier M: Similarities and perspectives on the two C's-Cancer and COVID-19. J Thromb Haemost *19(5)*: 1161-1167, 2021. PMID: 33725410. DOI: 10.1111/jth.15294

16 Bakouny Z, Hawley JE, Choueiri TK, Peters S, Rini BI, Warner JL and Painter CA: COVID-19 and cancer: Current challenges and perspectives. Cancer Cell *38(5)*: 629-646, 2020. PMID: 33049215. DOI: 10.1016/j.ccell.2020.09.018

17 Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, Le Mao R, Rodríguez C, Hunt BJ and Monreal M: Incidence of VTE and bleeding among hospitalized patients with Coronavirus disease 2019: a systematic review and meta-analysis. Chest *159(3)*: 1182-1196, 2021. PMID: 33217420. DOI: 10.1016/j.chest.2020.11.005

18 Gratz J, Wiegele M, Maleczek M, Herkner H, Schöchl H, Chwala E, Knöbl P and Schaden E: Risk of clinically relevant venous thromboembolism in critically ill patients with COVID-19: a systematic review and meta-analysis. Front Med (Lausanne) *8*: 647917, 2021. PMID: 33768106. DOI: 10.3389/fmed.2021.647917

19 Zhang R, Ni L, Di X, Wang X, Ma B, Niu S and Liu C: Systematic review and meta-analysis of the prevalence of venous thromboembolic events in novel coronavirus disease-2019 patients. J Vasc Surg Venous Lymphat Disord *9(2)*: 289-298.e5, 2021. PMID: 33309903. DOI: 10.1016/j.jvsv.2020.11.023

20 Porfidia A, Valeriani E, Pola R, Porreca E, Rutjes AWS and Di Nisio M: Venous thromboembolism in patients with COVID-19: Systematic review and meta-analysis. Thromb Res *196*: 67-74, 2020. PMID: 32853978. DOI: 10.1016/j.thromres.2020.08.020

21 Spyropoulos AC and Weitz JI: Hospitalized COVID-19 patients and venous thromboembolism: a perfect storm. Circulation *142(2)*: 129-132, 2020. PMID: 32658609. DOI: 10.1161/CIRCULATIONAHA.120.048020

22 Tan BK, Mainbourg S, Friggeri A, Bertoletti L, Douplat M, Dargaud Y, Grange C, Lobbes H, Provencher S and Lega JC: Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. Thorax *76(10)*: 970-979, 2021. PMID: 33622981. DOI: 10.1136/thoraxjnl-2020-215383

23 Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI and van Es N: Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost *18(8)*: 1995-2002, 2020. PMID: 32369666. DOI: 10.1111/jth.14888

24 Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ and Jonigk D: Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med *383(2)*: 120-128, 2020. PMID: 32437596. DOI: 10.1056/NEJMoa2015432

25 Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J and Ogeng'o J: Arterial thrombosis in Coronavirus disease 2019 patients: a rapid systematic review. Ann Vasc Surg *70*: 273-281, 2021. PMID: 32866574. DOI: 10.1016/j.avsg.2020.08.087

26 Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R and Clary B: Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine *29*: 100639, 2020. PMID: 33251499. DOI: 10.1016/j.eclinm.2020.100639

27 Ahmed S, Zimba O and Gasparyan AY: Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol *39(9)*: 2529-2543, 2020. PMID: 32654082. DOI: 10.1007/s10067-020-05275-1

28 Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C and Pöhlmann S: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell *181(2)*: 271-280.e8, 2020. PMID: 32142651. DOI: 10.1016/j.cell.2020.02.052

29 Razeghian-Jahromi I, Zibaeenezhad MJ, Lu Z, Zahra E, Mahboobeh R and Lionetti V: Angiotensin-converting enzyme 2: a double-edged sword in COVID-19 patients with an increased risk of heart failure. Heart Fail Rev *26(2)*: 371-380, 2021. PMID: 32844337. DOI: 10.1007/s10741-020-10016-2

30 Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, Bolling MC, Dijkstra G, Voors AA, Osterhaus AD, van der Voort PH, Mulder DJ and van Goor H: Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol *251(3)*: 228-248, 2020. PMID: 32418199. DOI: 10.1002/path.5471

31 Libby P and Lüscher T: COVID-19 is, in the end, an endothelial disease. Eur Heart J *41(32)*: 3038-3044, 2020. PMID: 32882706. DOI: 10.1093/eurheartj/ehaa623

32 Moore P, Esmail F, Qin S, Nand S and Berg S: Hypercoagulability of COVID-19 and neurological complications: a review. J Stroke Cerebrovasc Dis *31(1)*: 106163, 2022. PMID: 34763262. DOI: 10.1016/j.jstrokecerebrovasdis.2021.106163

33 Marchetti M: COVID-19-driven endothelial damage: complement, HIF-1, and ABL2 are potential pathways of damage and targets for cure. Ann Hematol *99(8)*: 1701-1707, 2020. PMID: 32583086. DOI: 10.1007/s00277-020-04138-8

34 Chen AT, Wang CY, Zhu WL and Chen W: Coagulation disorders and thrombosis in COVID-19 patients and a possible mechanism involving endothelial cells: a review. Aging Dis *13(1)*: 144-156, 2022. PMID: 35111367. DOI: 10.14336/AD.2021.0704

35 Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F and CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and

Sepsis Trial Group for Global Evaluation and Research in Sepsis): High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med *46(6)*: 1089-1098, 2020. PMID: 32367170. DOI: 10.1007/s00134-020-06062-x

36 Smadja DM, Mentzer SJ, Fontenay M, Laffan MA, Ackermann M, Helms J, Jonigk D, Chocron R, Pier GB, Gendron N, Pons S, Diehl JL, Margadant C, Guerin C, Huijbers EJM, Philippe A, Chapuis N, Nowak-Sliwinska P, Karagiannidis C, Sanchez O, Kümpers P, Skurnik D, Randi AM and Griffioen AW: COVID-19 is a systemic vascular hemopathy: insight for mechanistic and clinical aspects. Angiogenesis *24(4)*: 755-788, 2021. PMID: 34184164. DOI: 10.1007/s10456-021-09805-6

37 Van Dreden P, Fraser DD, Voiriot G, Rousseau A, Elalamy I, Prassas I, Terpos E, Dimopoulos MA, Grusse M and Gerotziafas GT: The compass-COVID-19-ICU study: Identification of factors to predict the risk of intubation and mortality in patients with severe Covid-19. Blood *138(Suppl 1)*: 2121, 2021. DOI: 10.1182/blood-2021-146483

38 Pancaldi E, Pascariello G, Cimino G, Cersosimo A, Amore L, Alghisi F, Bernardi N, Calvi E, Lombardi CM, Vizzardi E and Metra M: Thrombotic risk in patients with COVID-19. Rev Cardiovasc Med *22(2)*: 277-286, 2021. PMID: 34258896. DOI: 10.31083/j.rcm2202035

39 Petito E, Falcinelli E, Paliani U, Cesari E, Vaudo G, Sebastiano M, Cerotto V, Guglielmini G, Gori F, Malvestiti M, Becattini C, Paciullo F, De Robertis E, Bury L, Lazzarini T, Gresele P and COVIR study investigators: Association of neutrophil activation, more than platelet activation, with thrombotic complications in Coronavirus disease 2019. J Infect Dis *223(6)*: 933-944, 2021. PMID: 33280009. DOI: 10.1093/infdis/jiaa756

40 Gerotziafas GT, Papageorgiou L, Salta S, Nikolopoulou K and Elalamy I: Updated clinical models for VTE prediction in hospitalized medical patients. Thromb Res *164(Suppl 1)*: S62-S69, 2018. PMID: 29703486. DOI: 10.1016/j.thromres.2018.02.004

41 Gerotziafas GT, Catalano M, Colgan MP, Pecsvarady Z, Wautrecht JC, Fazeli B, Olinic DM, Farkas K, Elalamy I, Falanga A, Fareed J, Papageorgiou C, Arellano RS, Agathagelou P, Antic D, Auad L, Banfic L, Bartolomew JR, Benczur B, Bernardo MB, Boccardo F, Cifkova R, Cosmi B, De Marchi S, Dimakakos E, Dimopoulos MA, Dimitrov G, Durand-Zaleski I, Edmonds M, El Nazar EA, Erer D, Esponda OL, Gresele P, Gschwandtner M, Gu Y, Heinzmann M, Hamburg NM, Hamadé A, Jatoi NA, Karahan O, Karetova D, Karplus T, Klein-Weigel P, Kolossvary E, Kozak M, Lefkou E, Lessiani G, Liew A, Marcoccia A, Marshang P, Marakomichelakis G, Matuska J, Moraglia L, Pillon S, Poredos P, Prior M, Salvador DRK, Schlager O, Schernthaner G, Sieron A, Spaak J, Spyropoulos A, Sprynger M, Suput D, Stanek A, Stvrtinova V, Szuba A, Tafur A, Vandreden P, Vardas PE, Vasic D, Vikkula M, Wennberg P, Zhai Z and Scientific Reviewer Committee: Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: Position paper from VAS-European Independent Foundation in Angiology/Vascular Medicine. Thromb Haemost *120(12)*: 1597-1628, 2020. PMID: 32920811. DOI: 10.1055/s-0040-1715798

42 Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, Douketis JD and Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis: Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost *18(8)*: 1859-1865, 2020. PMID: 32459046. DOI: 10.1111/jth.14929

43 Goldin M, Lin SK, Kohn N, Qiu M, Cohen SL, Barish MA, Gianos E, Diaz A, Richardson S, Giannis D, Chatterjee S, Coppa K, Hirsch JS, Ngu S, Firoozan S, McGinn T and Spyropoulos AC: External validation of the IMPROVE-DD risk assessment model for venous thromboembolism among inpatients with COVID-19. J Thromb Thrombolysis *52(4)*: 1032-1035, 2021. PMID: 34146235. DOI: 10.1007/s11239-021-02504-5

44 Spyropoulos AC, Cohen SL, Gianos E, Kohn N, Giannis D, Chatterjee S, Goldin M, Lesser M, Coppa K, Hirsch JS, McGinn T, Barish MA and COVID□19 Consortium Group: Validation of the IMPROVE-DD risk assessment model for venous thromboembolism among hospitalized patients with COVID-19. Res Pract Thromb Haemost *5(2)*: 296-300, 2021. PMID: 33733028. DOI: 10.1002/rth2.12486

45 Gerotziafas GT, Sergentanis TN, Voiriot G, Lassel L, Papageorgiou C, Elabbadi A, Turpin M, Vandreden P, Papageorgiou L, Psaltopoulou T, Terpos E, Dimopoulos MA, Parrot A, Cadranel J, Pialoux G, Fartoukh M and Elalamy I: Derivation and validation of a predictive score for disease worsening in patients with COVID-19. Thromb Haemost *120(12)*: 1680-1690, 2020. PMID: 32961572. DOI: 10.1055/s-0040-1716544

46 Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, DeSancho MT, Diuguid DL, Griffin DO, Kahn SR, Klok FA, Lee AI, Neumann I, Pai A, Righini M, Sanfilippo K, Siegal DM, Skara M, Terrell DR, Touri K, Akl EA, Al Jabiri RN, Al Jabiri YN, Barbara AM, Bognanni A, Boulos M, Brignardello-Petersen R, Charide R, Colunga-Lozano LE, Dearness KL, Darzi AJ, Hussein H, Karam SG, Mansour R, Morgano GP, Morsi RZ, Muti-Schünemann G, Nadim MK, Philip BA, Qiu Y, Benitez YR, Stevens A, Solo K, Wiercioch W, Mustafa RA and Schünemann HJ: American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. Blood Adv: 2022007561, 2022. PMID: 35503027. DOI: 10.1182/bloodadvances.2022007561

47 Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, Holley AB, Iaccarino J, Jimenez D, LeGal G, Rali P and Wells P: Thromboprophylaxis in patients with COVID-19: a brief update to the CHEST Guideline and Expert Panel report. Chest, 2022. PMID: 35167861. DOI: 10.1016/j.chest.2022.02.006

48 Kollias A, Kyriakoulis KG, Trontzas IP, Rapti V, Kyriakoulis IG, Theochari CA, Dimakakos E, Poulakou G and Syrigos K: High *versus* standard intensity of thromboprophylaxis in hospitalized patients with COVID-19: a systematic review and meta-analysis. J Clin Med *10(23)*: 5549, 2021. PMID: 34884258. DOI: 10.3390/jcm10235549

49 Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, Mignatti A, Gianos E, Cohen M, Sharifova G, Lund JM, Tafur A, Lewis PA, Cohoon KP, Rahman H, Sison CP, Lesser ML, Ochani K, Agrawal N, Hsia J, Anderson VE, Bonaca M, Halperin JL, Weitz JI and HEP-COVID Investigators: Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: The HEP-COVID randomized clinical

trial. JAMA Intern Med *181(12)*: 1612-1620, 2021. PMID: 34617959. DOI: 10.1001/jamainternmed.2021.6203

50 Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, Alomran F, Alayed K, Alsheef M, AlSumait F, Pompilio CE, Sperlich C, Tangri S, Tang T, Jaksa P, Suryanarayan D, Almarshoodi M, Castellucci LA, James PD, Lillicrap D, Carrier M, Beckett A, Colovos C, Jayakar J, Arsenault MP, Wu C, Doyon K, Andreou ER, Dounaevskaia V, Tseng EK, Lim G, Fralick M, Middeldorp S, Lee AYY, Zuo F, da Costa BR, Thorpe KE, Negri EM, Cushman M, Jüni P and RAPID trial investigators: Effectiveness of therapeutic heparin *versus* prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ *375*: n2400, 2021. PMID: 34649864. DOI: 10.1136/bmj.n2400

51 ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, Gong MN, Carrier M, Rosenson RS, Reynolds HR, Turgeon AF, Escobedo J, Huang DT, Bradbury CA, Houston BL, Kornblith LZ, Kumar A, Kahn SR, Cushman M, McQuilten Z, Slutsky AS, Kim KS, Gordon AC, Kirwan BA, Brooks MM, Higgins AM, Lewis RJ, Lorenzi E, Berry SM, Berry LR, Aday AW, Al-Beidh F, Annane D, Arabi YM, Aryal D, Baumann Kreuziger L, Beane A, Bhimani Z, Bihari S, Billett HH, Bond L, Bonten M, Brunkhorst F, Buxton M, Buzgau A, Castellucci LA, Chekuri S, Chen JT, Cheng AC, Chkhikvadze T, Coiffard B, Costantini TW, de Brouwer S, Derde LPG, Detry MA, Duggal A, Džavík V, Effron MB, Estcourt LJ, Everett BM, Fergusson DA, Fitzgerald M, Fowler RA, Galanaud JP, Galen BT, Gandotra S, García-Madrona S, Girard TD, Godoy LC, Goodman AL, Goossens H, Green C, Greenstein YY, Gross PL, Hamburg NM, Haniffa R, Hanna G, Hanna N, Hegde SM, Hendrickson CM, Hite RD, Hindenburg AA, Hope AA, Horowitz JM, Horvat CM, Hudock K, Hunt BJ, Husain M, Hyzy RC, Iyer VN, Jacobson JR, Jayakumar D, Keller NM, Khan A, Kim Y, Kindzelski AL, King AJ, Knudson MM, Kornblith AE, Krishnan V, Kutcher ME, Laffan MA, Lamontagne F, Le Gal G, Leeper CM, Leifer ES, Lim G, Lima FG, Linstrum K, Litton E, Lopez-Sendon J, Lopez-Sendon Moreno JL, Lother SA, Malhotra S, Marcos M, Saud Marinez A, Marshall JC, Marten N, Matthay MA, McAuley DF, McDonald EG, McGlothlin A, McGuinness SP, Middeldorp S, Montgomery SK, Moore SC, Morillo Guerrero R, Mouncey PR, Murthy S, Nair GB, Nair R, Nichol AD, Nunez-Garcia B, Pandey A, Park PK, Parke RL, Parker JC, Parnia S, Paul JD, Pérez González YS, Pompilio M, Prekker ME, Quigley JG, Rost NS, Rowan K, Santos FO, Santos M, Olombrada Santos M, Satterwhite L, Saunders CT, Schutgens REG, Seymour CW, Siegal DM, Silva DG Jr, Shankar-Hari M, Sheehan JP, Singhal AB, Solvason D, Stanworth SJ, Tritschler T, Turner AM, van Bentum-Puijk W, van de Veerdonk FL, van Diepen S, Vazquez-Grande G, Wahid L, Wareham V, Wells BJ, Widmer RJ, Wilson JG, Yuriditsky E, Zampieri FG, Angus DC, McArthur CJ, Webb SA, Farkouh ME, Hochman JS and Zarychanski R: Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. N Engl J Med *385(9)*: 790-802, 2021. PMID: 34351721. DOI: 10.1056/NEJMoa2105911

52 Capell WH, Barnathan ES, Piazza G, Spyropoulos AC, Hsia J, Bull S, Lipardi C, Sugarmann C, Suh E, Rao JP, Hiatt WR and Bonaca MP: Rationale and design for the study of rivaroxaban to reduce thrombotic events, hospitalization and death in outpatients with COVID-19: The PREVENT-HD study. Am Heart J *235*: 12-23, 2021. PMID: 33577800. DOI: 10.1016/j.ahj.2021.02.001

53 Barco S, Bingisser R, Colucci G, Frenk A, Gerber B, Held U, Mach F, Mazzolai L, Righini M, Rosemann T, Sebastian T, Spescha R, Stortecky S, Windecker S and Kucher N: Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus disease-2019 (the OVID study): a structured summary of a study protocol for a randomized controlled trial. Trials *21(1)*: 770, 2020. PMID: 32907635. DOI: 10.1186/s13063-020-04678-4

54 Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, Lins Dos Santos J, Volpiani GG, Sobreira ML, Joviliano EE, Bohatch Júnior MS, da Fonseca BAL, Ribeiro MS, Dusilek C, Itinose K, Sanches SMV, de Almeida Araujo Ramos K, de Moraes NF, Tierno PFGMM, de Oliveira ALML, Tachibana A, Chate RC, Santos MVB, de Menezes Cavalcante BB, Moreira RCR, Chang C, Tafur A, Fareed J, Lopes RD and MICHELLE investigators: Rivaroxaban *versus* no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet *399(10319)*: 50-59, 2022. PMID: 34921756. DOI: 10.1016/S0140-6736(21)02392-8

55 Metharom P, Falasca M and Berndt MC: The history of Armand Trousseau and cancer-associated thrombosis. Cancers (Basel) *11(2)*: 158, 2019. PMID: 30708967. DOI: 10.3390/cancers11020158

56 Canale ML, Bisceglia I, Lestuzzi C, Parrini I and ANMCO Cardio-Oncology Task Force: Arterial thrombosis in cancer: Spotlight on the neglected vessels. Anticancer Res *39(9)*: 4619-4625, 2019. PMID: 31519559. DOI: 10.21873/anticanres.13642

57 Abdol Razak NB, Jones G, Bhandari M, Berndt MC and Metharom P: Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. Cancers (Basel) *10(10)*: 380, 2018. PMID: 30314362. DOI: 10.3390/cancers10100380

58 Wun T and White RH: Epidemiology of cancer-related venous thromboembolism. Best Pract Res Clin Haematol *22(1)*: 9-23, 2009. PMID: 19285269. DOI: 10.1016/j.beha.2008.12.001

59 Elyamany G, Alzahrani AM and Bukhary E: Cancer-associated thrombosis: an overview. Clin Med Insights Oncol *8*: 129-137, 2014. PMID: 25520567. DOI: 10.4137/CMO.S18991

60 Robertson L, Yeoh SE, Broderick C, Stansby G and Agarwal R: Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE. Cochrane Database Syst Rev *11*: CD010837, 2018. PMID: 30407621. DOI: 10.1002/14651858.CD010837.pub4

61 Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, Panageas KS and DeAngelis LM: Risk of arterial thromboembolism in patients with cancer. J Am Coll Cardiol *70(8)*: 926-938, 2017. PMID: 28818202. DOI: 10.1016/j.jacc.2017.06.047

62 Chu AJ: Tissue factor, blood coagulation, and beyond: an overview. Int J Inflam *2011*: 367284, 2011. PMID: 21941675. DOI: 10.4061/2011/367284

63 Mackman N: The role of tissue factor and factor VIIa in hemostasis. Anesth Analg *108(5)*: 1447-1452, 2009. PMID: 19372318. DOI: 10.1213/ane.0b013e31819bceb1

64 Rondon AMR, Kroone C, Kapteijn MY, Versteeg HH and Buijs JT: Role of tissue factor in tumor progression and cancer-associated thrombosis. Semin Thromb Hemost *45(4)*: 396-412, 2019. PMID: 31096312. DOI: 10.1055/s-0039-1687895

65 Doyle LM and Wang MZ: Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation

and analysis. Cells *8(7)*: 727, 2019. PMID: 31311206. DOI: 10.3390/cells8070727

66 Hisada Y and Mackman N: Tissue factor and extracellular vesicles: Activation of coagulation and impact on survival in cancer. Cancers (Basel) *13(15)*: 3839, 2021. PMID: 34359742. DOI: 10.3390/cancers13153839

67 Spronk HM, ten Cate H and van der Meijden PE: Differential roles of tissue factor and phosphatidylserine in activation of coagulation. Thromb Res *133(Suppl 1)*: S54-S56, 2014. PMID: 24759145. DOI: 10.1016/j.thromres.2014.03.022

68 Tamura S, Suzuki-Inoue K, Tsukiji N, Shirai T, Sasaki T, Osada M, Satoh K and Ozaki Y: Podoplanin-positive periarteriolar stromal cells promote megakaryocyte growth and proplatelet formation in mice by CLEC-2. Blood *127(13)*: 1701-1710, 2016. PMID: 26796360. DOI: 10.1182/blood-2015-08-663708

69 Meng D, Luo M and Liu B: The role of CLEC-2 and its ligands in thromboinflammation. Front Immunol *12*: 688643, 2021. PMID: 34177942. DOI: 10.3389/fimmu.2021.688643

70 Riedl J, Preusser M, Nazari PM, Posch F, Panzer S, Marosi C, Birner P, Thaler J, Brostjan C, Lötsch D, Berger W, Hainfellner JA, Pabinger I and Ay C: Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. Blood *129(13)*: 1831-1839, 2017. PMID: 28073783. DOI: 10.1182/blood-2016-06-720714

71 Gagliano N, Celesti G, Tacchini L, Pluchino S, Sforza C, Rasile M, Valerio V, Laghi L, Conte V and Procacci P: Epithelial-to-mesenchymal transition in pancreatic ductal adenocarcinoma: Characterization in a 3D-cell culture model. World J Gastroenterol *22(18)*: 4466-4483, 2016. PMID: 27182158. DOI: 10.3748/wjg.v22.i18.4466

72 Demers M, Krause DS, Schatzberg D, Martinod K, Voorhees JR, Fuchs TA, Scadden DT and Wagner DD: Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. Proc Natl Acad Sci USA *109(32)*: 13076-13081, 2012. PMID: 22826226. DOI: 10.1073/pnas.1200419109

73 Mahajan A, Brunson A, Adesina O, Keegan THM and Wun T: The incidence of cancer-associated thrombosis is increasing over time. Blood Adv *6(1)*: 307-320, 2022. PMID: 34649273. DOI: 10.1182/bloodadvances.2021005590

74 Gerotziafas GT, Mahé I, Lefkou E, AboElnazar E, Abdel-Razeq H, Taher A, Antic D, Elalamy I, Syrigos K and Van Dreden P: Overview of risk assessment models for venous thromboembolism in ambulatory patients with cancer. Thromb Res *191(Suppl 1)*: S50-S57, 2020. PMID: 32736779. DOI: 10.1016/S00493848(20)30397-2

75 Dimakakos E, Livanios K, Vathiotis I, Gomatou G, Gkiozos I, Kotteas E, Kainis E and Syrigos K: Risk factors for venous thromboembolism in patients with small cell lung cancer. Anticancer Res *41(3)*: 1523-1528, 2021. PMID: 33788745. DOI: 10.21873/anticanres.14911

76 Agnelli G, Bolis G, Capussotti L, Scarpa RM, Tonelli F, Bonizzoni E, Moia M, Parazzini F, Rossi R, Sonaglia F, Valarani B, Bianchini C and Gussoni G: A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg *243(1)*: 89-95, 2006. PMID: 16371741. DOI: 10.1097/01.sla.0000193959.44677.48

77 Murray J, Precious E and Alikhan R: Catheter-related thrombosis in cancer patients. Br J Haematol *162(6)*: 748-757, 2013. PMID: 23848991. DOI: 10.1111/bjh.12474

78 Debbie Jiang MD and Alfred Ian Lee MD: Thrombotic risk from chemotherapy and other cancer therapies. Cancer Treat Res *179*: 87-101, 2019. PMID: 31317482. DOI: 10.1007/978-3-030-20315-3_6

79 Tuzovic M, Herrmann J, Iliescu C, Marmagkiolis K, Ziaeian B and Yang EH: Arterial thrombosis in patients with cancer. Curr Treat Options Cardiovasc Med *20(5)*: 40, 2018. PMID: 29627870. DOI: 10.1007/s11936-018-0635-x

80 Kim AS, Khorana AA and McCrae KR: Mechanisms and biomarkers of cancer-associated thrombosis. Transl Res *225*: 33-53, 2020. PMID: 32645431. DOI: 10.1016/j.trsl.2020.06.012

81 Khorana AA, Kuderer NM, Culakova E, Lyman GH and Francis CW: Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood *111(10)*: 4902-4907, 2008. PMID: 18216292. DOI: 10.1182/blood-2007-10-116327

82 Dimakakos E, Kotteas E, Gomatou G, Katsarou T, Vlahakos V, Vathiotis I, Talagani S, Dimitroulis I and Syrigos K: Do we need prophylactic anticoagulation in ambulatory patients with lung cancer? A review. Vasc Med *25(3)*: 255-262, 2020. PMID: 32146869. DOI: 10.1177/1358863X19899160

83 Gerotziafas GT, Taher A, Abdel-Razeq H, AboElnazar E, Spyropoulos AC, El Shemmari S, Larsen AK, Elalamy I and COMPASS–CAT Working Group: A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: The prospective COMPASS-Cancer-Associated Thrombosis study. Oncologist *22(10)*: 1222-1231, 2017. PMID: 28550032. DOI: 10.1634/theoncologist.2016-0414

84 Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, Quehenberger P, Zielinski C and Pabinger I: Prediction of venous thromboembolism in cancer patients. Blood *116(24)*: 5377-5382, 2010. PMID: 20829374. DOI: 10.1182/blood-2010-02-270116

85 Verso M, Agnelli G, Barni S, Gasparini G and LaBianca R: A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med *7(3)*: 291-292, 2012. PMID: 22547369. DOI: 10.1007/s11739-012-0784-y

86 Pelzer U, Sinn M, Stieler J and Riess H: [Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?]. Dtsch Med Wochenschr *138(41)*: 2084-2088, 2013. PMID: 24085361. DOI: 10.1055/s-0033-1349608

87 van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahé I, Wilts IT, Twint DC, Porreca E, Arrieta O, Stépanian A, Smit K, De Tursi M, Bleker SM, Bossuyt PM, Nieuwland R, Kamphuisen PW and Büller HR: Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica *102(9)*: 1494-1501, 2017. PMID: 28550192. DOI: 10.3324/haematol.2017.169060

88 Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH and Falanga A: Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline update. J Clin Oncol *38(5)*: 496-520, 2020. PMID: 31381464. DOI: 10.1200/JCO.19.01461

89 Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, Kuruvilla P, Hill D, Spadafora S, Marquis K, Trinkaus M, Tomiak A, Lee AYY, Gross PL, Lazo-Langner A, El-Maraghi R, Goss G, Le Gal G, Stewart D, Ramsay T, Rodger M, Witham D, Wells PS and AVERT Investigators: Apixaban to prevent venous

thromboembolism in patients with cancer. N Engl J Med *380(8)*: 711-719, 2019. PMID: 30511879. DOI: 10.1056/NEJMoa1814468

90 Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T, Streiff MB, Garcia DA, Liebman HA, Belani CP, O'Reilly EM, Patel JN, Yimer HA, Wildgoose P, Burton P, Vijapurkar U, Kaul S, Eikelboom J, McBane R, Bauer KA, Kuderer NM, Lyman GH and CASSINI Investigators: Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med *380(8)*: 720-728, 2019. PMID: 30786186. DOI: 10.1056/NEJMoa1814630

91 Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, Leavitt AD, Lee AYY, Macbeth F, Morgan RL, Noble S, Sexton EA, Stenehjem D, Wiercioch W, Kahale LA and Alonso-Coello P: American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv *5(4)*: 927-974, 2021. PMID: 33570602. DOI: 10.1182/bloodadvances.2020003442

92 Li JY, Wang HF, Yin P, Li D, Wang DL, Peng P, Wang WH, Wang L, Yuan XW, Xie JY, Zhou F, Xiong N, Shao F, Wang CX, Tong X, Ye H, Wan WJ, Liu BD, Li WZ, Li Q, Tang LV, Hu Y, Lip GYH and Thrombo-COVID-19 Collaborative: Clinical characteristics and risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: A multicenter retrospective study. J Thromb Haemost *19(4)*: 1038-1048, 2021. PMID: 33534149. DOI: 10.1111/jth.15261

93 Patell R, Bogue T, Bindal P, Koshy A, Merrill M, Aird WC, Bauer KA and Zwicker JI: Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. J Thromb Haemost *18(9)*: 2349-2357, 2020. PMID: 32692862. DOI: 10.1111/jth.15018

94 Fenioux C, Allenbach Y, Vozy A, Salem JÉ, Maalouf G, Vieira M, Le Joncour A, Benveniste O, Saadoun D, Frère C, Campedel L, Salem P, Gligorov J, Funck-Brentano C, Cacoub P and Gougis P: [Differences of characteristics and outcomes between cancer patients and patients with no active cancer hospitalised for a SARS-CoV-2 infection]. Bull Cancer *108(6)*: 581-588, 2021. PMID: 33966886. DOI: 10.1016/j.bulcan.2021.03.004

95 Obispo B, Rogado J, Muñoz-Rivas N, Pangua C, Serrano G, Lara MA and Infanta Leonor Thrombosis Research Group: Prevalence of thrombosis in patients with cancer and SARS-CoV-2 infection. Med Clin (Barc), 2021. PMID: 34674859. DOI: 10.1016/j.medcli.2021.08.002

96 Paredes-Ruiz D, Gómez-Cuervo C, Gómez-Martín C, Sánchez-Guerrero Á, González-Olmedo J, López-López F, Bover-Larroya M, Yarza-Barrio R, Jara-Casas DD, Castelo-Laureiro A, Revilla-Ostolaza Y, Paz-Ares L, Lumbreras-Bermejo C and Díaz-Pedroche C: Incidence of venous thromboembolism in patients with non-hematological cancer admitted for COVID-19 at a third-level hospital in Madrid. J Thromb Thrombolysis *53(2)*: 471-478, 2022. PMID: 33890200. DOI: 10.1007/s11239-021-02448-w

97 Zavras PD, Mehta V, Goel S, Pradhan K and Billett HH: Increased incidence of thrombosis in a cohort of cancer patients with COVID-19. Acta Haematol *145(2)*: 152-159, 2022. PMID: 34666332. DOI: 10.1159/000519292

98 Li A, Kuderer NM, Hsu CY, Shyr Y, Warner JL, Shah DP, Kumar V, Shah S, Kulkarni AA, Fu J, Gulati S, Zon RL, Li M, Desai A, Egan PC, Bakouny Z, Kc D, Hwang C, Akpan IJ, McKay RR, Girard J, Schmidt AL, Halmos B, Thompson MA, Patel JM, Pennell NA, Peters S, Elshoury A, de Lima Lopes G, Stover DG, Grivas P, Rini BI, Painter CA, Mishra S, Connors JM, Lyman GH, Rosovsky RP and CCC19 consortium: The CoVID-TE risk assessment model for venous thromboembolism in hospitalized patients with cancer and COVID-19. J Thromb Haemost *19(10)*: 2522-2532, 2021. PMID: 34260813. DOI: 10.1111/jth.15463

99 Rogado J, Obispo B, Muñoz-Rivas N, Lara MA and Infanta Leonor Thrombosis Research Group: Incidence of thromboembolic events in cancer hospitalized patients with COVID-19. Chest *159(6)*: 2512-2513, 2021. PMID: 34099141. DOI: 10.1016/j.chest.2021.01.022

100 Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, Chackathayil J, Cheng VW, Curley HM, Fittall MW, Freeman-Mills L, Gennatas S, Goel A, Hartley S, Hughes DJ, Kerr D, Lee AJ, Lee RJ, McGrath SE, Middleton CP, Murugaesu N, Newsom-Davis T, Okines AF, Olsson-Brown AC, Palles C, Pan Y, Pettengell R, Powles T, Protheroe EA, Purshouse K, Sharma-Oates A, Sivakumar S, Smith AJ, Starkey T, Turnbull CD, Várnai C, Yousaf N, UK Coronavirus Monitoring Project Team., Kerr R and Middleton G: COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet *395(10241)*: 1919-1926, 2020. PMID: 32473682. DOI: 10.1016/S0140-6736(20)31173-9

101 Whisenant JG, Baena J, Cortellini A, Huang LC, Lo Russo G, Porcu L, Wong SK, Bestvina CM, Hellmann MD, Roca E, Rizvi H, Monnet I, Boudjemaa A, Rogado J, Pasello G, Leighl NB, Arrieta O, Aujayeb A, Batra U, Azzam AY, Unk M, Azab MA, Zhumagaliyeva AN, Gomez-Martin C, Blaquier JB, Geraedts E, Mountzios G, Serrano-Montero G, Reinmuth N, Coate L, Marmarelis M, Presley CJ, Hirsch FR, Garrido P, Khan H, Baggi A, Mascaux C, Halmos B, Ceresoli GL, Fidler MJ, Scotti V, Métivier AC, Falchero L, Felip E, Genova C, Mazieres J, Tapan U, Brahmer J, Bria E, Puri S, Popat S, Reckamp KL, Morgillo F, Nadal E, Mazzoni F, Agustoni F, Bar J, Grosso F, Avrillon V, Patel JD, Gomes F, Ibrahim E, Trama A, Bettini AC, Barlesi F, Dingemans AM, Wakelee H, Peters S, Horn L, Garassino MC, Torri V and TERAVOLT study group: A definitive prognostication system for patients with thoracic malignancies diagnosed with Coronavirus disease 2019: An update from the TERAVOLT registry. J Thorac Oncol *17(5)*: 661-674, 2022. PMID: 35121086. DOI: 10.1016/j.jtho.2021.12.015

102 Curigliano G, Banerjee S, Cervantes A, Garassino MC, Garrido P, Girard N, Haanen J, Jordan K, Lordick F, Machiels JP, Michielin O, Peters S, Tabernero J, Douillard JY, Pentheroudakis G and Panel members: Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol *31(10)*: 1320-1335, 2020. PMID: 32745693. DOI: 10.1016/j.annonc.2020.07.010

103 Patriarcheas V, Pikoulas A, Kostis M, Charpidou A and Dimakakos E: Heparin-induced thrombocytopenia: Pathophysiology, diagnosis and management. Cureus *12(3)*: e7385, 2020. PMID: 32337112. DOI: 10.7759/cureus.7385

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