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Venous thromboembolism risk, prophylaxis and management in cancer patients with COVID-19: An unmet medical need

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ABSTRACT

Cancer patients exhibit an increased risk of venous thromboembolism (VTE), with VTE being the second leading cause of morbidity and mortality in these patients. The implementation of lockdowns following the COVID-19 pandemic has resulted in decreased mobility and delayed access to care, thus further increasing the susceptibility to VTE. Cancer patients may also be at a higher risk of SARS-CoV-2 infection and have been shown to be more likely to experience severe COVID-19 disease compared to patients without cancer. Given that both cancer and COVID-19 exhibit a hypercoagulable state, stasis of blood flow, and endothelial injury, cancer patients with COVID-19 constitute a vulnerable population with a high risk of thrombosis and bleeding. However, to date there are limited studies evaluating whether cancer patients infected with SARS-CoV-2 have a higher VTE incidence than COVID-19 patients without cancer, how to assess the risk of VTE, prophylaxis and treatment in this special population. Herein, we highlight the urgent need for studies in cancer patients with COVID-19 to ensure appropriate patient care and improve clinical outcomes.

Patients with cancer have an increased risk of venous thromboembolism (VTE) with thromboembolism being the second leading cause of mortality in patients with cancer [1]. Appropriate prophylaxis and management of VTE in cancer patients is complex as the VTE risk is dependent upon patient demographics, their medical history, the type and stage of the malignancy and the type of cancer treatment [2]. In addition, cancer patients who have already had an event of acute VTE are at an increased risk of recurrent events. The implementation of lockdowns following the COVID-19 pandemic has resulted in decreased mobility and delayed access to care [3], which might further increase the susceptibility to VTE. Optimal prophylaxis and treatment of VTE in cancer patients is further complicated if they are infected with SARS-CoV-2 and develop respiratory complications.

Clinical manifestations of COVID-19 range from mild disease with asymptomatic features to severe acute respiratory distress and multiple organ dysfunction syndrome (MODS) that may lead to death [4]. To date, several mechanisms have been proposed to explain COVID-19-associated MODS but growing evidence points toward the role of hypercoagulation, and a high prevalence of micro- and macro-circulatory thrombosis has been reported to trigger morbidity and mortality in critically ill COVID-19 patients [5].

The risk of thromboembolism in COVID-19 has been observed to vary with disease progression, with increased hypercoagulability in more severe COVID-19 cases. Several risk factors seem to be associated with

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progression into severe forms of COVID-19 including age, gender, and pre-existing comorbidities such as cardiovascular, lung, kidney and central nervous system diseases, diabetes, obesity and cancer [6,7]. The VTE risk is also significantly higher among patients admitted to the intensive care unit (ICU) versus non-ICU hospitalised patients. For instance, one study showed VTE occurred in 22.7% [95% CI, 18.1–27.6] of COVID-19 patients in the ICU, compared to 7.9% [95% CI, 5.1–11.2] of COVID-19 patients hospitalised in the conventional wards. Similarly, pulmonary embolism (PE) was observed in 13.7% and 3.5% of ICU and non-ICU patients respectively [8].

Both cancer and COVID-19 exhibit a hypercoagulable state, stasis of blood flow, and endothelial injury [9]. While the pathophysiological mechanisms leading to thrombosis in cancer patients [10] are distinct from those in COVID-19 patients [11], there are commonalities and both cancer and COVID-19 increase the risk of VTE. Proinflammatory cytokines, including tumour necrosis factor-α and interleukin 1, are induced by both COVID-19 and cancer and are significant contributors in the development of thrombosis in both clinical scenarios [12]. Given that both cancer and COVID-19 exhibit hypercoagulation and altered haematological parameters, an increased incidence of VTE or bleeding in cancer patients with COVID-19 cannot be discounted. Thus, patients that have both cancer and COVID-19 constitute a unique population that requires special attention for thrombosis risk management. Recently, a risk assessment model named CoVID-TE has been derived for VTE in hospitalized patients with COVID-19 and cancer to stratify patients into different VTE risk groups at the time of admission. The risk assessment model can serve as a real-time clinical decision support tool once it is externally validated [13].

1. VTE risk in cancer patients with COVID-19

Only few studies have so far assessed the VTE incidence in cancer versus non-cancer patients with COVID-19. A small retrospective cohort study in patients hospitalised with COVID-19 (45 cancer patients and 353 patients without cancer), reported no difference in VTE occurrence between cancer and non-cancer patients [14]. However, a recent larger retrospective cohort study including 5556 COVID-19-positive patients (of which 421 were cancer patients) reported that cancer patients were more likely to be hospitalised upon COVID-19 infection and to develop VTE compared to their non-cancer counterparts ($OR_{adj} = 1.77$, 95% CI = 1.01 to 3.09) [15]. No difference was however observed in terms of ICU admission or mortality [15]. A preliminary analysis from a cohort study based on electronic medical records from University Medical Center in New Orleans suggested a possible synergistic effect between COVID-19 and cancer which further increased the risk of VTE in these patients [16]. More studies including larger number of cancer-COVID-19 patients and evaluating the VTE risk and consequences of COVID-19 in different cancer populations are needed.

As the risk of thromboembolism in COVID-19 has been observed to vary with disease progression, it is also important to consider the risk of cancer patients developing severe forms of COVID-19. A meta-analysis of 20 studies showed that patients with cancer were 76% more likely to experience severe disease compared to those without cancer [17]. Among patients with cancer, those with haematological malignancies had a more severe course of COVID-19 than those with solid tumours (OR 1.57, 95% CI 1.15–2.15; $p < 0.0043$) [18]. Compared to the rest of the United Kingdom coronavirus Cancer Monitoring Project (UKCCMP) cohort, patients with leukaemia had an increased case-fatality rate (OR 2.25, 1.13–4.57; $p = 0.023$) [18]. A worse outcome in patients with haematological malignancies and COVID-19, compared to patients who had either COVID-19 alone or haematological malignancies alone was also reported in an Italian retrospective multi-centre study [19].

2. Prophylaxis and VTE management in cancer patients with COVID-19

Although several recommendations have been made by international organisations with respect to cancer care [20] during the COVID-19 era and anticoagulation treatment in COVID-19 patients [21–25], no international guidelines exist to direct clinicians on anticoagulation use in patients that have both cancer and COVID-19.

Currently, the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) [26] is the only one to provide specific guidelines on anticoagulant use in both ambulatory and hospitalised cancer patients with COVID-19 as per the WHO clinical progression scale [27]. These guidelines strongly support the use of prophylactic doses of LMWH in ambulatory cancer patients with COVID-19 and in hospitalised cancer patients with mild to severe COVID-19. While they marginally support the use of intermediate LMWH doses in mild hospitalised cases, they moderately support the use of intermediate doses in severe hospitalised cases and therapeutic doses of LMWH or UFH in intubated patients. Therapeutic doses of UFH is strongly recommended in reducing the mortality in cancer patients with COVID-19 that are on extracorporeal membrane oxygenation.

Although bleeding events related to COVID-19 are uncommon [28], studies evaluating the bleeding risk are warranted to make a more informed decision on the use of prophylactic versus therapeutic doses of anticoagulants in cancer patients with COVID-19.

Additionally, studies are warranted to better understand whether early initiation of thromboprophylaxis in cancer patients with COVID-19 would alter the disease progression and their need for hospitalisation.

It is important to note that no recommendations have been made with respect to extended thromboprophylaxis in cancer patients with COVID-19, leaving behind an important unmet medical gap in the recommendations for this special population who is vulnerable to progress into severe forms of disease and recurrent VTE.

Anticoagulant treatment decisions in cancer patients with COVID-19 should be made upon a careful risk-benefit evaluation and should take into account all the parameters that are normally assessed in non-COVID-19 cancer patients such as individual patient factors, type of malignancy and cancer treatment. Dose and duration of anticoagulants are some of the important factors that need to be carefully evaluated to ensure the best possible clinical outcomes in this special population.

3. Perspectives and conclusions

To date, there are few studies that have evaluated the interplay of cancer and COVID-19. Although some studies have recently highlighted the long-term clinical effects of COVID-19, evidence of the clinical course of COVID-19-associated thrombosis and its long-term effects on the morbidity and mortality of patients with cancer is scarce. Future studies are warranted to enhance the knowledge of VTE risk, prophylaxis and treatment in this unique population. Moreover, although several guidelines exist on the initiation or continuation of cancer therapies during the COVID-19 pandemic, specific guidance on VTE prophylaxis and treatment in patients with both cancer and COVID-19 is largely missing. Such guidance would be essential to ensure appropriate patient care and better clinical outcomes in cancer patients with COVID-19.

Author contribution statement

All authors have contributed to the preparation of this manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Benjamin Brenner received personal fees for participation in advisory

boards and for lectures from Bayer, Pfizer, Sanofi, ROVI Pharmaceuticals, and Leo Pharma; honoraria from Hikma pharmaceuticals and Sanofi. Cihan Ay received personal fees for participation in advisory boards and for lectures from Bayer, BMS/Pfizer, Daiichi/Sankyo, and Sanofi. Grégoire Le Gal holds the Chair on Diagnosis of Venous Thromboembolism, Department of Medicine, University of Ottawa and have received a mid-career clinician-scientist award from the Heart and Stroke Foundation of Canada. Marc Carrier received funding for research from BMS, Pfizer, and Leo Pharma and personal fees from Bayer, BMS, Pfizer, Sanofi, Servier, and Leo Pharma. Andrés J. Muñoz is Head of Cancer & Thrombosis Section of the Spanish Society of Medical Oncology (SEOM) and Coordinator of TESEO-SEOM Registry of cancer-associated thrombosis, and received consulting fees from Sanofi, BMS, Leo Pharma, Pfizer, Astrazeneca. Also received honoraria from Rovi, Bayer, Daichii-Sankyo and travel grant from Roche, Amgen and Merck. Giancarlo Agnelli reports personal fees from Werfen, Bristol Myers Squibb, Pfizer, Bayer Healthcare, and Daichi Sankyo outside the submitted work. Ana Thereza Rocha received personal fees for participation in advisory boards and for lectures from Bayer, Daiichi/Sankyo, Boehringer Ingelheim and Sanofi. Hikmat Abdel-Razeq has nothing to report. Ismail Elalamy received research funding and personal fees for participation in advisory boards and for lectures from Bayer, BMS/Pfizer, LeoPharma, Aspen, Boehringer Ingelheim, Sanofi and ROVI Pharmaceuticals. Anna Falanga is a full professor of Hematology at the University of Milan Bicocca and Director of the Department of Transfusion Medicine and Hematology in Bergamo, Italy. Received honoraria from Werfen, Stago, Bayer, Leo Pharma, Sanofi and Rovi.

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References

[1] A.A. Khorana, Venous thromboembolism and prognosis in cancer, Thromb. Res. 125 (6) (2010) 490–493, https://doi.org/10.1016/j.thromres.2009.12.023.
[2] W. Qureshi, Z. Ali, W. Amjad, Z. Alirhayim, H. Farooq, S. Qadir, et al., Venous thromboembolism in cancer: an update of treatment and prevention in the era of newer anticoagulants, Front Cardiovasc Med 3 (2016) 24, https://doi.org/10.3389/fcvm.2016.00024.
[3] C. Maringe, J. Spicer, M. Morris, A. Purushotham, E. Nolte, R. Sullivan, et al., The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study, Lancet Oncol. 21 (8) (2020) 1023–1034, https://doi.org/10.1016/S1470-2045(20)30388-0.
[4] M. Cascella, M. Rajnik, A. Cuomo, S.C. Dulebohn, R. Di Napoli, Features, Evaluation and Treatment Coronavirus (COVID-19), StatPearls. Treasure Island (FL, 2020.
[5] T. Iba, J.H. Levy, M. Levi, J.M. Connors, J. Thachil, Coagulopathy of coronavirus disease 2019, Crit. Care Med. (2020), https://doi.org/10.1097/CCM.0000000000004458.
[6] R.E. Jordan, P. Adab, K.K. Cheng, Covid-19: risk factors for severe disease and death, BMJ 368 (2020) m1198, https://doi.org/10.1136/bmj.m1198.
[7] C. Edler, A.S. Schroder, M. Aepfelbacher, A. Fitzek, A. Heinemann, F. Heinrich, et al., Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany, Int. J. Leg. Med. 134 (4) (2020) 1275–1284, https://doi.org/10.1007/s00414-020-02317-w.
[8] S. Nopp, F. Moik, B. Jilma, I. Pabinger, C. Ay, Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis, Res Pract Thromb Haemost (2020), https://doi.org/10.1002/rth2.12439.
[9] J. Thachil, A. Khorana, M. Carrier, Similarities and perspectives on the two C's - cancer and COVID-19, J. Thromb. Haemostasis (2021), https://doi.org/10.1111/jth.15294.
[10] M. Mukai, T. Oka, Mechanism and management of cancer-associated thrombosis, J. Cardiol. 72 (2) (2018) 89–93, https://doi.org/10.1016/j.jjcc.2018.02.011.
[11] T. Iba, J.H. Levy, J.M. Connors, T.E. Warkentin, J. Thachil, M. Levi, The unique characteristics of COVID-19 coagulopathy, Crit. Care 24 (1) (2020) 360, https://doi.org/10.1186/s13054-020-03077-0.
[12] N.A. Horowitz, B. Brenner, Thrombosis and hemostasis issues in cancer patients with COVID-19, Semin. Thromb. Hemost. 46 (7) (2020) 785–788, https://doi.org/10.1055/s-0040-1714275.
[13] A. Li, N.M. Kuderer, C.-Y. Hsu, Y. Shyr, J.L. Warner, D.P. Shah, et al., the CCC19 consortium, The CoVID-TE risk assessment model for venous thromboembolism in hospitalized patients with cancer and COVID-19, J Thromb Haemost. 19 (10) (2021) 2522–2532, https://doi.org/10.1111/jth.15463.
[14] R. Patell, T. Bogue, P. Bindal, A. Koshy, M. Merrill, W.C. Aird, et al., Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19, J. Thromb. Haemostasis (2020), https://doi.org/10.1111/jth.15018.
[15] N. Alpert, J.L. Rapp, B. Marcellino, W. Lieberman-Cribbin, R. Flores, E. Taioli, Clinical course of cancer patients with COVID-19: a retrospective cohort study, JNCI Cancer Spectr. 5 (1) (2021), pkaa085, https://doi.org/10.1093/jncics/pkaa085.
[16] A. Ananthula, D. Tran, K. Thomas, K.L.M.M. Amaker, A. Nguyen, S. Mahato, et al., Association and prevalence of venous thromboembolism in cancer patients with COVID-19: A single healthcare system experience, J. Clin. Oncol. 39 (15_suppl) (2021) 2627, https://doi.org/10.1200/JCO.2021.39.15_suppl.2627.
[17] R. Ofori-Asenso, O. Ogundipe, A.A. Agyeman, K.L. Chin, M. Mazidi, Z. Ademi, et al., Cancer is associated with severe disease in COVID-19 patients: a systematic review and meta-analysis, Ecancermedicalscience 14 (2020) 1047, https://doi.org/10.3332/ecancer.2020.1047.
[18] L.Y.W. Lee, J.B. Cazier, T. Starkey, S.E.W. Briggs, R. Arnold, V. Bisht, et al., COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study, Lancet Oncol. 21 (10) (2020) 1309–1316, https://doi.org/10.1016/S1470-2045(20)30442–3.
[19] F. Passamonti, C. Cattaneo, L. Arcaini, R. Bruna, M. Cavo, F. Merli, et al., Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study, Lancet Haematol 7 (10) (2020) e737–e745, https://doi.org/10.1016/S2352-3026(20)30251-9.
[20] A. Tartarone, R. Lerose, COVID-19 and cancer care: what do international guidelines say? Med. Oncol. 37 (9) (2020) 80, https://doi.org/10.1007/s12032-020-01406-5.
[21] A. Casini, L. Alberio, A. Angelillo-Scherrer, P. Fontana, B. Gerber, L. Graf, et al., Thromboprophylaxis and laboratory monitoring for in-hospital patients with COVID-19 - a Swiss consensus statement by the Working Party Hemostasis, Swiss Med. Wkly. 150 (2020) w20247, https://doi.org/10.4414/smw.2020.20247.
[22] G.D. Barnes, A. Burnett, A. Allen, M. Blumenstein, N.P. Clark, A. Cuker, et al., Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum, J. Thromb. Thrombolysis 50 (1) (2020) 72–81, https://doi.org/10.1007/s11239-020-02138-z.
[23] M. Oudkerk, H.R. Buller, D. Kuijpers, N. van Es, S.F. Oudkerk, T.C. McLoud, et al., Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the national institute for public health of The Netherlands, Radiology (2020), 201629, https://doi.org/10.1148/radiol.2020201629.
[24] D. Vivas, V. Roldan, M.A. Esteve-Pastor, I. Roldan, A. Tello-Montoliu, J.M. Ruiz-Nodar, et al., Recommendations on antithrombotic treatment during the COVID-19 pandemic. Position statement of the working group on cardiovascular thrombosis of the Spanish society of cardiology, Rev. Esp. Cardiol. (2020), https://doi.org/10.1016/j.rec.2020.04.025.
[25] Clinical Management of COVID-19, 2020 [press release].
[26] N. Giesen, R. Sprute, M. Ruthrich, Y. Khodamoradi, S.C. Mellinghoff, G. Beutel, et al., Evidence-based management of COVID-19 in cancer patients: guideline by the infectious diseases working party (AGIHO) of the German society for Haematology and medical Oncology (DGHO), Eur. J. Cancer 140 (2020) 86–104, https://doi.org/10.1016/j.ejca.2020.09.009.
[27] WHO, A minimal common outcome measure set for COVID-19 clinical research, Lancet Infect. Dis 20 (8) (2020), https://doi.org/10.1016/S1473-3099(20)30483-7.
[28] C.B. Conti, S. Henchi, G.P. Coppeta, S. Testa, R. Grassia, Bleeding in COVID-19 severe pneumonia: the other side of abnormal coagulation pattern? Eur. J. Intern. Med. 77 (2020) 147–149, https://doi.org/10.1016/j.ejim.2020.05.002.