Cancer patients and COVID-19: Mortality, serious complications, biomarkers, and ways forward

Kush Gupta [a,*], Shipra Gandhi [b], Alexander Mebane III [c], Angelica Singh [d], Nivetha Vishnuvardhan [d], Eshan Patel [d]

[a] Kasturba Medical College, Light House Hill Road, Mangalore, KA 575001, India
[b] Roswell Park Comprehensive Cancer Center, Buffalo, NY 14203, USA
[c] Heart, Vascular & Leg Center, 5020 Commerce Dr, Bakersfield, CA, 93309, USA
[d] NewYork-Presbyterian/Brooklyn Methodist Hospital, 506 6th Street, Brooklyn, New York, 11215 USA

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ABSTRACT

The SARS-CoV-2 (COVID-19) pandemic has particularly serious consequences for cancer patients, as they are at high risk for severe complications and mortality due to the virus since cancer patients are immunocompromised. Preliminary evidence suggests that patients with hematological, and metastatic malignancies are particularly susceptible to developing severe COVID-19 illness, which leads to poor prognosis. Biomarkers including C-reactive protein and interleukin-6 may be predictors of outcome and, therefore, crucial in assessing COVID-19 illness severity in cancer patients. A patient-specific risk and benefit inventory should be completed, and expert guidelines consulted when deciding to continue or postpone therapeutic interventions. This review presents preliminary evidence of COVID-19 infection and its impact on cancer, as well as discussion of general guidelines for the treatment and management of cancer patients with COVID-19.

Abbreviations

COVID-19,	Severe acute respiratory syndrome coronavirus 2
CI,	Confidence interval
CRP,	C-reactive protein
IL-6,	Interleukin-6
OR,	Odds ratio
COPD,	Chronic obstructive pulmonary disorder
tPA,	Tissue plasminogen activator
ARDS,	Acute respiratory distress syndrome
ACE2,	AngioteSnsin converting enzyme 2
ADAM17,	A disintegrin and metalloproteinase
RAAS,	Renin-angiotensin-aldosterone system
LMWH,	Low molecular weight heparin
ASH,	American Society of Hematology
BCG,	Bacille Calmette-Guérin

Introduction

Since the first outbreak of SARS-CoV-2 (COVID-19) was reported in December 2019, there have been over 52 million confirmed cases and 1282,000 deaths worldwide, with 241,000 deaths occurring in the United States [1]. Though scientific understanding of the virus is constantly evolving, there are a number of known risk factors for COVID-19 infection including male sex, chronic obstructive pulmonary disorder, hypertension, obesity, and certain cardiac comorbidities [2-4]. Notably, cancer patients also have a higher risk of COVID-19 infection, with a recent study reporting a hazard ratio of 3.56 (95% confidence interval [CI] 1.65–7.69) when compared to the general population [5]. Furthermore, several studies have documented a high rate of COVID-19-associated mortality in cancer patients [6, 7].

Due to health anxieties and desire to avoid viral exposure, some cancer patients have delayed or paused treatments [8]. Certain key biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), and others are being investigated for prognostic capability and treatment course determination in cancer patients with COVID-19 [9-11].

Guidelines are currently being developed to determine treatment priorities on the basis of risk stratifications [12-14]. This review presents preliminary evidence of COVID-19 and its impact on cancer, then discusses general guidelines for the treatment and management of cancer patients that have contracted COVID-19.

Cancer, COVID-19 infection, and mortality

Though there is some debate about the strength of evidence, reports generally suggest that cancer patients are more vulnerable to COVID-19 infection than the general population, perhaps due to their immunocompromised state. The previously referenced study by Liang et al., which reported a hazard ratio of 3.56 for COVID-19 infection among cancer patients [5], has been supported by several other studies. One retrospective cross-sectional study found that cancer patients have a two-fold higher COVID-19 infection rate in comparison to the general population (0.79% and 0.37%, respectively, odds ratio [OR] 2.31, 95% CI 1.89–3.02) [15]. Additionally, in their pooled analysis, de las Heras et al. found that 1.0–3.9% of COVID-positive patients had an underlying diagnosis of cancer; this range increased to 7.3–20.3% for COVID-positive patients who died or became seriously ill [6], which is much higher than the proportion of cancer patients in the general population.

Among cancer patients, some appear to be more vulnerable than others when it comes to COVID-19. A multicenter study showed that patients with hematologic, lung, or other metastatic malignancies, and those who had undergone surgical procedures were more vulnerable to serious COVID-19 illness [16]. This same study found that the general population and patients with non-metastatic cancer have a similar predisposition to serious COVID-19 illness [16]. In their retrospective cohort of 309 cancer patients, Jee et al. similarly found that lung and hematologic cancer patients had hazard ratios of 2.0 and 1.90, respectively, for severe or critical COVID-19 events [17]. Lee et al. also reported higher risk for severe COVID-19 illness for cancer patients with hematologic malignancies versus solid tumors [18]. They also found that case-fatality rate for cancer patients with COVID-19 rose significantly with increasing age [18], echoing a trend seen in the general population. In sum, COVID-19 does not appear to affect all cancer patients equally.

Not only are cancer patients at risk for severe COVID-19 illness, they are also at high risk for mortality. A mathematical dynamic model from researchers in Latin America estimated the COVID-19-related mortality rate in cancer patients to be between 18.4–30.4% [19]; yet according to some studies, these estimates appear to be somewhat low. Following a nosocomial outbreak of COVID-19 in a hematological oncology unit in Central Europe, 36.8% of their patients died [7]; nearly a third (30.6%) of the 1044 patients in the UK Cancer Coronavirus Monitoring Project died, the vast majority of whom (92.5%) had cause of death recorded as COVID-19 [18]. Another study by Sanchez-Pina et al., reported that patients with hematologic malignancies had COVID-related mortality of 35.9% versus 13.2% in COVID-positive, non-cancer, age- and illness-severity-matched controls ($p = 0.003$, OR 6.652) [9]; and in a retrospective chart review of 1878 COVID-19 patients, 52.3% (9/17) of the lung cancer patients died compared to just 10.2% COVID-19 mortality in the general population at the same center ($p<0.0001$), though it should be noted that a majority of the lung cancer patients had metastatic malignancy (11/17) and comorbidities such as hypertension (10/17) and chronic obstructive pulmonary disorder (COPD) (9/17) [20]. Regardless, these numbers illustrate how severe COVID-19 infection can be for cancer patients.

Cardiovascular complications in COVID-positive cancer patients

One particular area of concern is cardiovascular complications observed in cancer patients with COVID-19. Cardiovascular complications are a common feature of COVID-19 infection [21-24] and include conditions such as embolism, stroke, cardiac injuries, and arrythmias [21, 25-27]. Likewise, it is well known that cancer and cancer treatments promote various cardiovascular complications and coagulopathies [28]; indeed, both cancer and COVID-19 infection in isolation fulfill Virchow's triad for thrombosis by involving blood stasis, vascular wall damage, and hypercoagulation states [29], so it follows that COVID-19 infection further exacerbates these complications in cancer patients. One prospective cohort study provides strong evidence in favor of this hypothesis, indicating that COVID-positive cancer patients with cardiovascular disease have an odds ratio for mortality of 2.32 (95% confidence interval of 1.47–3.64) compared to COVID-positive cancer patients without comorbidities [30].

The mechanism of synergy between COVID-19 infection and cancer leading to cardiovascular complication is not clear; but it may be via hyperinflammation, which negatively affects the cardiovascular system. Excessive activation of innate and adaptive immune cells causes a dysregulated immune response and can promote cardiovascular and endothelial dysfunction [31]. For example, in response to inflammation, neutrophils mobilize their chromatin extracellularly to form neutrophilic extracellular traps (NETs), which encourages a thrombophilic state [32, 33]. Venous and arterial thrombosis is one of the key risk factors for developing critical illnesses in COVID-19 patients and often presents as skin rashes [34-37] or chilblain-like lesions on the hands and feet [38], sometimes referred to as "COVID toes."

In cancer patients, it is necessary to proactively avoid the occurrence of life-threatening coagulopathies and hyperinflammation with prophylactic therapies. Fibrinolytic interventional therapy using tissue plasminogen activator (tPA) has been indicated to be beneficial when used as a rescue therapy in patients who have acute respiratory distress syndrome (ARDS) due to COVID-19 [39]. Low molecular weight heparin and other anticoagulants should also be contemplated as a prophylactic measure in cancer patients with COVID-19 infection, as they have been effective in preventing thrombosis in cancer patients previously [40-42]. Nevertheless, these exploratory measures should be considered in the context of mixed evidence, as one retrospective cohort of 398 subjects found similar rates of thrombotic and hemorrhagic events in cancer and non-cancer cohorts [43].

Renin-angiotensin-aldosterone system (RAAS) and COVID-positive cancer patients

The SARS-CoV-2 virus utilizes the angiotensin converting enzyme 2 (ACE2) receptor for entry by engaging its spike proteins [44]. The ACE2 receptor is present in a wide variety of cell types and tissues [45] and has the primary function of hydrolyzing Angiotensin-II (a vasoconstrictive peptide) into Angiotensin (1–7), which then acts as a vasodilator. In this way, it acts as a counterbalance for ACE, which cleaves Angiotensin-I into Angiotensin-II. During excessive inflammation, ACE2 receptors can also be downregulated by metalloproteases called a disintegrin and metalloproteinase (ADAM17) [46, 47]. This process may decrease ACE2 expression from cell surfaces, thus causing an imbalance to the renin-angiotensin-aldosterone system (RAAS) and adding to endothelial dysfunctions. For this reason, some have proposed that the inhibition of ADAM17 may play a protective role in COVID-19 by maintaining the surface expression of ACE2 [48].

RAAS has a role in cancer biology by remodeling the tumor microenvironment and influencing tumor growth and dissemination [49], though the exact role is debated; a review by Rosenthal and Gavras indicates that evidence for ACE inhibitors' effect on cancer is mixed, though as an adjuvant therapy they may be beneficial for cancer patient outcomes [50]. In certain studies, angiotensin system inhibitors have been beneficial in treating non-metastatic cancer patients by activating the immune response [49, 51]. The dysregulation of RAAS system during COVID-19 infection can further complicate some of the treatment aspects in cancer patients where ACE blockers are anticipated to have better prognosis.

Key biomarkers for COVID-19 illness in cancer patients

There may be certain biomarkers that indicate severe COVID-19 illness in cancer patients, so it is prudent to base treatment guidelines on this developing evidence.

C-reactive protein (CRP) is an important marker of endothelial dysfunction during inflammation due to infection and chronic cardiovascular disorders [52, 53]. CRP levels can be used to indicate the severity of the COVID-19 infection, as evidenced by multiple studies [10, 54-56]. These levels may be especially useful in prognosis for COVID-positive cancer patients, as a study by Sanchez-Pina et al. found that CRP >10 mg/dl was significantly correlated with significantly higher odds of COVID-related mortality (13.56, $p = 0.03$) in patients with leukemia, myeloma, and lymphoma [9]. Therefore, CRP should be given consideration as a prognostic marker in cancer patients during the course of treatment for COVID-19 illness.

Interleukin-6 (IL-6) is a proinflammatory cytokine that plays a key role in fever and acute immune response, as well as governs the release of CRP from the liver [53]. IL-6 has been shown to play a crucial role during severe COVID-19 infection and has a reliable prognostic value [56-58]. Blocking IL-6 in cancer patients has been demonstrated to be beneficial when combined with other conventional therapies [59]. Blocking IL-6 can be achieved through an antibody called tocilizumab [60], which has also been shown to reduce inflammation and decrease the mortality rate in COVID-19 patients [61]. However, blocking this pathway may also contribute to the immunocompromised state and increase the chances of secondary infection [62], or produce other off-target effects. One case report of two COVID-19 patients who received tocilizumab cautions against its use, as both patients progressed to hemophagocytic lymphohistiocytosis [63], a highly fatal disease characterized by overproduction of immune cells. Due to IL-6′s independent correlation with cancer and COVID-19 infection as well as its close relation to CRP, IL-6 deserves consideration (and additional trials) as a potential prognostic indicator for cancer patients with COVID-19 illness.

Treatment guidelines for COVID-positive cancer patients

Guidelines are under development for treating cancer patients in the COVID-19 era, with researchers proffering methods for both treating cancer and treating COVID-19 in cancer patients who already have been infected by the virus, as well as methods for reducing risk of virus contraction in un-infected cancer patients.

Evidence regarding initiation of chemotherapy in COVID patients is largely mixed. In a retrospective cohort of 309 cancer patients, Jee et al. found that cytotoxic chemotherapy administration within 35 days of COVID-19 diagnosis was not associated with severe or critical COVID-19 illness in cancer patients [17]. Another study came to similar conclusions, as cancer patients who received chemotherapy within 4 weeks of their COVID-19 diagnosis were at no greater risk for mortality than cancer patients who had not received chemotherapy in the same time period [30]. By contrast, yet another study found that after adjusting for age and sex, patients with hematologic malignancies who had recently undergone chemotherapy had 2.09 times the odds of in-hospital COVID-related death [18]. With varied and limited evidence, it is difficult to make definitive suggestions for chemotherapy treatment with confidence in this population of cancer patients with COVID infection.

Another area of concern and debate involves treatment delay for cancer patients in the COVID-19 era. One retrospective chart review of 165 lung cancer patients found that 9.1% had their cancer treatments delayed during the COVID-19 pandemic, with further analysis revealing that 80.0% of the time, this was at the patient's request instead of the doctor's or family's [8]. In July of 2020, additional guidelines developed by 32 radiotherapy experts were published regarding best practices for treating various types of lung cancer. Despite anxieties patients may feel, they generally recommended standard treatments so as not to worsen cancer-related prognosis — making an exception to postpone treatment for lung cancer patients infected with COVID-19 [64]. Liao et al. offer similar guidance based on their experience, endorsing that delays or altered treatment may be beneficial for cancer patients [65]. Notably, delays in certain treatments may have unknown effects for cancer patients undergoing multiple therapies at once, such as prostate cancer patients who may pause in-hospital radiotherapy at the risk of making concomitant androgen deprivation therapy less effective [66].

A variety of therapeutic options have been mentioned in other studies, though none with overwhelming support. In Rogado et al.'s retrospective chart review, they proposed that hydroxychloroquine and azithromycin were effective treatments for cancer patients with COVID-19, but only 6 patients were treated with this regimen [20]; in contrast, a study by the COVID-19 and Cancer Consortium of 1035 cancer patients with COVID-19 infection found that hydroxychloroquine and azithromycin were independent factors associated with increased 30-day mortality, though confounding could not be excluded [67]. Others have recommended administration of oral anticoagulants and low molecular weight heparin (LMWH) to avoid thrombotic events [29]. Though this recommendation is based on sound reasoning and backed by World Health Organization guidelines [68], there is a lack of trial-based evidence to support these therapies in COVID-positive cancer patients. In the non-malignant section of the American Society of Hematology (ASH) guidelines, they likewise endorses the prophylactic use of LMWH but specifies that therapeutic anticoagulation is not necessary for COVID-19 patients [69]. For patients with malignancies, ASH recommendations were more varied and often did not specify therapeutic anticoagulation measures [69]. Another study noted that countries that implemented universal BCG vaccination for tuberculosis had better outcomes for COVID-19 prevalence and mortality, which, incidentally, is also standard immunotherapy for select types of cancer [70]. Multiple trials are underway to investigate whether BCG could be an effective COVID-19 prophylactic for the general population, and for cancer patients in particular. Though positron emission tomography (PET) scans are not commonly used to manage patients with COVID-19, one study asserted based on their experience with a COVID-positive cancer patient that this imaging could be useful [71]. All of these therapeutic options discussed here merit further investigation.

There appears to be a consensus based on literature review, regarding the adoption of simple screening tools to prevent transmission of COVID19 infection in cancer patients. In their report, Assi et al. laud their tiered screening tools to identify asymptomatic carriers among cancer patients over more "sophisticated" methods such as reverse transcriptase PCR and computed tomography (CT) scans, which they say can be costly and ultimately less effective [72]. Global evidence of screening strategies abounds in the literature, with a study by Tang et al. describing high-, intermediate-, and low-risk categories to prevent nosocomial infection in Chinese hospitals using brief questionnaires [13]; Italian hospitals categorizing cancer patients as "active status" or "follow-up" to better prioritize resources and reduce risk of virus contraction during non-urgent hospital visits [14]; and a cancer center in Singapore detailing nosocomial infection prevention methods in their medical, radiation, imaging, and surgical oncology divisions of their cancer center [73]. Preliminary evidence from these studies indicates that screening and prevention methods have been highly successful in reducing viral spread. With various screening tools based on best practices now having been implemented, additional study is needed to now determine scientifically which of these methods is most effective at preventing COVID-19 infection, especially for cancer patients.

Amidst the uncertainty, there is reason for optimism. Freeman and Mikhael provide a positive perspective on the current and future treatment of cancer patients, reporting the changes to cancer treatment happening during this pandemic (e.g., increased emphasis on telehealth) could result in more effective, less expensive treatment in times beyond the current crisis [74].

Conclusion

Cancer patients have an elevated risk for COVID-19 infection and, if contracted, also have high risk of serious complications and death as a result. Based on evidence gathered from a number of studies, various biomarkers such as CRP and IL-6 should be considered to formulate a reliable assessment of COVID-19 illness severity in cancer patients. Developing a clearer understanding of the viral pathophysiology and effectiveness of various treatments will ultimately ameliorate the impact of COVID-19 in cancer patients. Survivors of cancer and COVID illness are a true testament to resilience, serving as a reminder that we can face uncertainty and accept the challenge to continually improve care for cancer patients with COVID-19.

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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.

References

[1] John Hopkins coronavirus resource center. [https://coronavirus.jhu.edu/map.html].

[2] J.M. Jin, P. Bai, W. He, F. Wu, X.F. Liu, D.M. Han, S. Liu, J.K. Yang, Gender differences in patients with COVID-19: focus on severity and mortality, Front Public Health 8 (2020) 152.

[3] L. Lan, D. Xu, G. Ye, C. Xia, S. Wang, Y. Li, H. Xu, Positive RT-PCR test results in patients recovered from COVID-19, JAMA 323 (15) (2020) 1502–1503, 21.

[4] J. Zhang, X. Wang, X. Jia, J. Li, K. Hu, G. Chen, J. Wei, Z. Gong, C. Zhou, H. Yu, et al., Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China, Clin. Microbiol. Infect. 26 (6) (2020) 767–772.

[5] W. Liang, W. Guan, R. Chen, W. Wang, J. Li, K. Xu, C. Li, Q. Ai, W. Lu, H. Liang, et al., Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China, Lancet Oncol. 21 (3) (2020) 335–337.

[6] B. de Las Heras, K.S. Saini, F. Boyle, F. Ades, E. de Azambuja, I. Bozovic-Spasojevic, M. Romano, M. Capelan, R. Prasad, P. Pattu, et al., Cancer treatment and research during the COVID-19 pandemic: experience of the first 6 months, Oncol. Ther. 8 (2) (2020) 171–182.

[7] M.M. Biernat, A. Zinczuk, P. Biernat, A. Bogucka-Fedorczuk, J. Kwiatkowski, E. Kalicinska, D. Marciniak, K. Simon, T. Wrobel, Nosocomial outbreak of SARS-CoV-2 infection in a haematological unit - High mortality rate in infected patients with haematologic malignancies, J. Clin. Virol. 130 (2020), 104574.

[8] K. Fujita, T. Ito, Z. Saito, O. Kanai, K. Nakatani, T. Mio, Impact of COVID-19 pandemic on lung cancer treatment scheduling, Thorac. Cancer (2020).

[9] J.M. Sanchez-Pina, M. Rodríguez Rodriguez, N. Castro Quismondo, R. Gil Manso, R. Colmenares, D. Gil Alos, M.L. Paciello, D. Zafra, C. Garcia-Sanchez, C. Villegas, et al., Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies, Eur. J. Haematol. (2020).

[10] F. Yang, S. Shi, J. Zhu, J. Shi, K. Dai, X. Chen, Clinical characteristics and outcomes of cancer patients with COVID-19, J. Med. Virol. (2020).

[11] T. Wu, Z. Zuo, S. Kang, L. Jiang, X. Luo, Z. Xia, J. Liu, X. Xiao, M. Ye, M. Deng, Multi-organ dysfunction in patients with COVID-19: a systematic review and meta-analysis, Aging Dis. 11 (4) (2020) 874–894.

[12] P.F. Stahel, How to risk-stratify elective surgery during the COVID-19 pandemic? Patient Saf. Surg. 14 (2020) 8.

[13] Z. Tang, B. Sun, B. Xu, A quick evaluation method of nosocomial infection risk for cancer hospitals during the COVID-19 pandemic, J. Cancer Res. Clin. Oncol. 146 (7) (2020) 1891–1892.

[14] M. Barba, E. Krasniqi, G. Ciliberto, P. Vici, Cancer patients and coronavirus disease 2019: evidence in context, J. Transl. Med. 18 (1) (2020).

[15] J. Yu, W. Ouyang, M.L.K. Chua, C. Xie, SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China, JAMA Oncol. (2020).

[16] M. Dai, D. Liu, M. Liu, F. Zhou, G. Li, Z. Chen, Z. Zhang, H. You, M. Wu, Q. Zheng, et al., Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak, Cancer Discov. 10 (6) (2020) 783–791.

[17] J. Jee, M.B. Foote, M. Lumish, A.J. Stonestrom, B. Wills, V. Narendra, V. Avutu, Y. R. Murciano-Goroff, J.E. Chan, A. Derkach, et al., Chemotherapy and COVID-19 outcomes in patients with cancer, J. Clin. Oncol. (2020). JCO.20.01307.

[18] L.Y.W. Lee, J.-.B. Cazier, T. Starkey, S.E.W. Briggs, R. Arnold, V. Bisht, S. Booth, N. A. Campton, V.W.T. Cheng, G. Collins, 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. (2020).

[19] A. Ruiz-Patino, O. Arrieta, L.E. Pino, C. Rolfo, L. Ricaurte, G. Recondo, Z. L. Zatarain-Barron, L. Corrales, C. Martin, F. Barron, et al., Mortality and advanced support requirement for patients with cancer with COVID-19: a mathematical dynamic model for Latin America, JCO Glob. Oncol. 6 (2020) 752–760.

[20] J. Rogado, C. Pangua, G. Serrano-Montero, B. Obispo, A.M. Marino, M. Pérez-Pérez, A. López-Alfonso, P. Gullón, M. Lara, Covid-19 and lung cancer: a greater fatality rate? Lung Cancer 146 (2020) 19–22.

[21] F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F. H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (2020) 145–147.

[22] C.M. Campbell, R. Kahwash, Will complement inhibition be the new target in treating COVID-19-related systemic thrombosis? Circulation 141 (22) (2020) 1739–1741.

[23] M. Madjid, P. Safavi-Naeini, S.D. Solomon, O. Vardeny, Potential effects of coronaviruses on the cardiovascular system: a review, JAMA Cardiol. (2020).

[24] E. Driggin, M.V. Madhavan, B. Bikdeli, T. Chuich, J. Laracy, G. Biondi-Zoccai, T. S. Brown, C. Der Nigoghossian, D.A. Zidar, J. Haythe, et al., Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic, J. Am. Coll. Cardiol. 75 (18) (2020) 2352–2371.

[25] A. Carpenter, O.J. Chambers, A. El Harchi, R. Bond, O. Hanington, S.C. Harmer, J. C. Hancox, A.F. James, COVID-19 management and arrhythmia: risks and challenges for clinicians treating patients affected by SARS-CoV-2, Front. Cardiovasc. Med. 7 (2020) 85.

[26] K.H. Kuck, Arrhythmias and sudden cardiac death in the COVID-19 pandemic, Herz 45 (4) (2020) 325–326.

[27] A.K. Mishra, K.K. Sahu, A. Lal, J. Sargent, Mechanisms of stroke and the role of anticoagulants in COVID-19, J. Formos. Med. Assoc. 119 (11) (2020) 1721–1722.

[28] V. Narayan, B. Ky, Common cardiovascular complications of cancer therapy: epidemiology, risk prediction, and prevention, Annu. Rev. Med. 69 (2018) 97–111.

[29] N.A. Horowitz, B. Brenner, Thrombosis and hemostasis issues in cancer patients with COVID-19, in: Seminars in Thrombosis and Hemostasis, 46, 2020, pp. 785–788.

[30] L.Y.W. Lee, J.B. Cazier, T. Starkey, C.D. Turnbull, UKCCMP Team, R. Kerr, G. Middleton, COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study, Lancet 395 (10241) (2020) 1919–1926.

[31] H.K. Mishra, J. Ma, B. Walcheck, Ectodomain shedding by ADAM17: its role in neutrophil recruitment and the impairment of this process during sepsis, Front. Cell Infect. Microbiol. 7 (2017) 138.

[32] J. Perdomo, H.H.L. Leung, Z. Ahmadi, F. Yan, J.J.H. Chong, F.H. Passam, B. H. Chong, Neutrophil activation and NETosis are the major drivers of thrombosis in heparin-induced thrombocytopenia, Nat. Commun. 10 (1) (2019) 1322.

[33] O.Z. Cheng, N. Palaniyar, NET balancing: a problem in inflammatory lung diseases, Front. Immunol. 4 (2013) 1.

[34] A.D. Blann, S. Dunmore, Arterial and venous thrombosis in cancer patients, Cardiol. Res. Pract. 2011 (2011), 394740.

[35] C. Magro, J.J. Mulvey, D. Berlin, G. Nuovo, S. Salvatore, J. Harp, A. Baxter-Stoltzfus, J. Laurence, Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases, Transl. Res. 220 (2020) 1–13.

[36] M.V. Mattoli, S. Taralli, E. Pennese, C. D'Angelo, F. Angrilli, C. Villano, Atypical presentation of COVID-19 incidentally detected at 18F-FDG PET/CT in an asymptomatic oncological patient, Clin. Nucl. Med. 45 (8) (2020) e383–e385.

[37] G. Tosti, A. Barisani, P. Queirolo, E. Pennacchioli, L. Villa, A.M. Lodeserto, S. Vaccari, Skin signs resembling vascular acrosyndromes during the COVID-19 outbreak in Italy, Clin. Exp. Dermatol. 45 (6) (2020) 757–758.

[38] N. Landa, M. Mendieta-Eckert, P. Fonda-Pascual, T. Aguirre, Chilblain-like lesions on feet and hands during the COVID-19 Pandemic, Int. J. Dermatol. 59 (6) (2020) 739–743.

[39] C.D. Barrett, A. Oren-Grinberg, E. Chao, A.H. Moraco, M.J. Martin, S.H. Reddy, A. M. Ilg, R. Jhunjhunwala, M. Uribe, H.B. Moore, et al., Rescue Therapy for severe COVID-19 associated Acute Respiratory Distress Syndrome (ARDS) with Tissue Plasminogen Activator (tPA): a case series, J. Trauma Acute Care Surg. (2020).

[40] R. Nassabein, B. Routy, N. Blais, J.P. Ayoub, M. Tehfe, Arterial thrombosis and coronavirus disease 2019 in a patient with cancer, Eur. J. Cancer 134 (2020) 1–2.

[41] H. Al-Samkari, J.M. Connors, The role of direct oral anticoagulants in treatment of cancer-associated thrombosis, Cancers (Basel) 10 (8) (2018).

[42] I. Fernandez-Ruiz, Apixaban therapy is effective and safe for cancer-associated VTE, Nat. Rev. Cardiol. 17 (6) (2020) 322.

[43] R. Patell, T. Bogue, P. Bindal, A. Koshy, M. Merrill, W.C. Aird, K.A. Bauer, J. I. Zwicker, Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19, J. Thromb. Haemost. 18 (9) (2020) 2349–2357.

[44] J. Shang, G. Ye, K. Shi, Y. Wan, C. Luo, H. Aihara, Q. Geng, A. Auerbach, F. Li, Structural basis of receptor recognition by SARS-CoV-2, Nature 581 (7807) (2020) 221–224.

[45] I. Hamming, W. Timens, M.L. Bulthuis, A.T. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2) (2004) 631–637.

[46] D.W. Lambert, M. Yarski, F.J. Warner, P. Thornhill, E.T. Parkin, A.I. Smith, N. M. Hooper, A.J. Turner, Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2), J. Biol. Chem. 280 (34) (2005) 30113–30119.

[47] A. Heurich, H. Hofmann-Winkler, S. Gierer, T. Liepold, O. Jahn, S. Pohlmann, TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein, J. Virol. 88 (2) (2014) 1293–1307.

[48] V. Palau, M. Riera, M.J. Soler, ADAM17 inhibition may exert a protective effect on COVID-19, Nephrol. Dial. Transplant. 35 (6) (2020) 1071–1072.

[49] M. Pinter, R.K. Jain, Targeting the renin-angiotensin system to improve cancer treatment: implications for immunotherapy, Sci. Transl. Med. 9 (410) (2017).

[50] T. Rosenthal, I. Gavras, Renin-angiotensin inhibition in combating malignancy: a review, Anticancer Res. 39 (9) (2019) 4597–4602.

[51] H. Liu, K. Naxerova, M. Pinter, J. Incio, H. Lee, K. Shigeta, W.W. Ho, J.A. Crain, A. Jacobson, T. Michelakos, et al., Use of angiotensin system inhibitors is associated with immune activation and longer survival in nonmetastatic pancreatic ductal adenocarcinoma, Clin. Cancer Res. 23 (19) (2017) 5959–5969.

[52] V. Selvaraju, P. Ayine, M. Fadamiro, J.R. Babu, M. Brown, T. Geetha, Urinary biomarkers of inflammation and oxidative stress are elevated in obese children and correlate with a marker of endothelial dysfunction, Oxid. Med. Cell. Longev. 2019 (2019) 1–10.

[53] S.M. Nehring, A. Goyal, P. Bansal, B.C. Patel, C Reactive Protein (CRP). In: StatPearls. edn., StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC., Treasure Island (FL), 2020.

[54] G. Wang, C. Wu, Q. Zhang, F. Wu, B. Yu, J. Lv, Y. Li, T. Li, S. Zhang, C. Wu, et al., C-Reactive protein level may predict the risk of COVID-19 aggravation, Open Forum. Infect. Dis. 7 (5) (2020) ofaa153.

[55] G. Wang, Q. Zhang, C. Wu, F. Wu, B. Yu, J. Lv, S. Zhang, G. Wu, Y. Zhong, Clinical characteristics of adult fevered COVID-19 patients and predictors for developing severe events, Front. Med. (Lausanne) 7 (2020) 324.

[56] F. Liu, L. Li, M. Xu, J. Wu, D. Luo, Y. Zhu, B. Li, X. Song, X. Zhou, Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19, J. Clin. Virol. 127 (2020) 104370.

[57] E. Grifoni, A. Valoriani, F. Cei, R. Lamanna, A.M.G. Gelli, B. Ciambotti, V. Vannucchi, F. Moroni, L. Pelagatti, R. Tarquini, et al., Interleukin-6 as prognosticator in patients with COVID-19, J. Infect. 81 (3) (2020) 452–482.

[58] Z.L. Zhang, Y.L. Hou, D.T. Li, F.Z. Li, Laboratory findings of COVID-19: a systematic review and meta-analysis, Scand J Clin Lab Invest (2020) 1–7.

[59] N. Kumari, B.S. Dwarakanath, A. Das, A.N. Bhatt, Role of interleukin-6 in cancer progression and therapeutic resistance, Tumour. Biol. 37 (9) (2016) 11553–11572.

[60] P. Rizzo, F. Vieceli Dalla Sega, F. Fortini, L. Marracino, C. Rapezzi, R. Ferrari, COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Basic Res Cardiol 115 (3) (2020) 31.

[61] C. Zhang, Z. Wu, J.W. Li, H. Zhao, G.Q. Wang, Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality, Int. J. Antimicrob. Agents. 55 (5) (2020), 105954.

[62] S. Antinori, C. Bonazzetti, G. Gubertini, A. Capetti, C. Pagani, V. Morena, S. Rimoldi, L. Galimberti, P. Sarzi-Puttini, A.L. Ridolfo, Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? Autoimmun. Rev. 19 (7) (2020), 102564.

[63] J. Radbel, N. Narayanan, P.J. Bhatt, Use of tocilizumab for COVID-19-induced cytokine release syndrome: a cautionary case report, Chest 158 (1) (2020) e15–e19.

[64] M. Guckenberger, C. Belka, A. Bezjak, J. Bradley, M.E. Daly, D. Deruysscher, R. Dziadziuszko, C. Faivre-Finn, M. Flentje, E. Gore, et al., Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: an ESTRO-ASTRO consensus statement, Int. J. Radiat. Oncol.*Biol.*Phys. 107 (4) (2020) 631–640.

[65] S. Liao, E. Rivin Del Campo, A. Salem, Q. Pang, H. Liu, J.L. Lopez Guerra, Optimizing lung cancer radiation treatment worldwide in COVID-19 outbreak, Lung Cancer 146 (2020) 230–235.

[66] S. Dee, B.A. Mahal, M.A. Arega, A.V. D'Amico, K.W. Mouw, P.L. Nguyen, V. Muralidhar, Relative timing of radiotherapy and androgen deprivation for prostate cancer and implications for treatment during the COVID-19 pandemic, JAMA Oncol. (2020).

[67] N.M. Kuderer, T.K. Choueiri, D.P. Shah, Y. Shyr, S.M. Rubinstein, D.R. Rivera, S. Shete, C.Y. Hsu, A. Desai, G. de Lima Lopes Jr, et al., Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study, Lancet 395 (10241) (2020) 1907–1918.

[68] R.J. Eck, W. Bult, J. Wetterslev, R.O.B. Gans, K. Meijer, F. Keus, I.C.C. van der Horst, Intermediate dose low-molecular-weight heparin for thrombosis prophylaxis: systematic review with meta-analysis and trial sequential analysis, Semin. Thromb. Hemost. 45 (8) (2019) 810–824.

[69] COVID-19 resources [https://www.hematology.org/covid-19].

[70] M. Koti, A. Morales, C.H. Graham, D.R. Siemens, BCG vaccine and COVID-19: implications for infection prophylaxis and cancer immunotherapy, J. Immunother. Cancer 8 (2) (2020), e001119.

[71] F. Ferrando-Castagnetto, C.G. Wakfie-Corieh, A.M.B. Garcia, M.G. Garcia-Esquinas, R.M.C. Caro, J.L.C. Delgado, Incidental and simultaneous finding of pulmonary thrombus and COVID-19 pneumonia in a cancer patient derived to (18)F-FDG PET/CT. New pathophysiological insights from hybrid imaging, Radiol. Case Rep. 15 (10) (2020) 1803–1805.

[72] T. Assi, B. Samra, L. Dercle, E. Rassy, J. Kattan, M. Ghosn, R. Houot, S. Ammari, Screening strategies for COVID-19 in patients with hematologic malignancies, Front. Oncol. (2020) 10.

[73] J. Chiang, V.S. Yang, S. Han, Q. Zhuang, G. Ooi, I.H. Sin, G.W.Y. Chua, S.Y. Tan, C. S. Chia, V.K. Tan, et al., Minimizing transmission of COVID-19 while delivering optimal cancer care in a National Cancer Centre, J. Cancer Policy 25 (2020), 100241.

[74] C.L. Freeman, J. Mikhael, COVID-19 and myeloma: what are the implications for now and in the future? Br. J. Haematol. 190 (2) (2020) 173–178.