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## Respiratory Medicine

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## Editorial

## Exploration of potential risk factors for COVID-19 severity in patients participating in oncology clinical trials



Coronavirus disease 2019 (COVID-19) has created the greatest threat to global health worldwide [1]. Several studies have claimed that cancer patients are highly susceptible to COVID-19 [2–4]. Various studies stated that comorbidities were associated with increased mortality in COVID-19 [5,6]. There is currently no promising guidance for conducting oncology clinical trials during the COVID-19 pandemic. Additionally, factors associated with the severity of COVID-19 could hamper the results of clinical trials. Therefore, our goal was to investigate potential risk factors for COVID-19 severity in patients participating in clinical cancer trials.

Senescent cells secrete a set of pro-inflammatory factors collectively called the senescence-associated secretory phenotype (SASP) [7]. The SASP includes several pro-inflammatory molecules, including TNF- $\alpha$ , IL-1 $\alpha/\beta$ , IL-6, IL-8, and chemokines (Ccl2, Cxcl10 and Ccl17) [8,9]. The SASP is considered a double-edged sword [10]. Short-term exposure to SASP can aid wound healing, which is crucial to the response to acute cell damage [11]. Conversely, long-term exposure to SASP can lead to damage to immune cells, triggering chronic inflammatory disease [12]. Several studies have claimed that cellular senescence is associated with the severity of COVID-19 in cancer patients [13–15]. Therefore, the cellular senescence status should be evaluated in patients participating in oncology clinical trials during the COVID-19 pandemic.

Due to the development of chemoresistance, cancer cells can still evade chemotherapy, which is a major barrier to cancer treatment [16]. Additionally, chemoresistance can increase metastasis, which makes it challenging to improve the clinical outcomes of cancer patients [17]. Preliminary studies have reported that chemoresistance is associated with the severity of COVID-19 in cancer patients [18,19]. Therefore, the chemoresistance status of cancer patients participating in clinical trials should be assessed during the COVID-19 pandemic.

COVID-19 targets the lungs; thus, patients with COVID-19 can develop various lung diseases, including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, moderate to severe asthma, and lung cancer [20]. On the other hand, several studies have stated that many types of heart disease, including coronary artery disease, cardiomyopathy, pulmonary hypertension, and congenital heart disease, are associated with the severity of COVID-19 in cancer patients [21–23]. Additionally, many studies have claimed that type 1 or type 2 diabetes could increase the complications of COVID-19 [24–26]. In addition, the type of clinical studies (screening/prevention, phases of trials) and kinds of treatment (cytotoxic chemotherapy, targeted therapy, immunotherapy, surgery, radiation) should be considered for clinical evaluation [27]. Taken together, the factors mentioned above should be evaluated for patients participating in oncology clinical trials during the COVID-19

pandemic.

Cytokines are a group of polypeptide signaling molecules that are essential for many biological processes [28]. However, several studies have claimed that elevated levels of cytokines and chemokines, such as IL-6, IL-2, IL-8, IL-4, IFN- $\gamma$ , CSF, VEGF, HGF, IP-10, MCP-1, and MIP 1- $\alpha$  are associated with complications of COVID-19 [28–30]. Elevated cytokines could be related to unsuitable inflammatory responses, triggering weak and inappropriate immune responses that need to be studied further for full clarification [31]. Therefore, to explain the potential impact of elevated cytokine levels in clinical trials during the COVID-19 pandemic, cytokine levels need to be effectively measured and characterized for patients participating in oncology clinical trials.

Rather than using an experimental agent, it is necessary to consider an approved COVID-19 vaccine for cancer patients participating in clinical studies. In addition, the dates of the first and second dose and possible side effects should be recorded. These data may help to evaluate the efficacy and safety of the COVID-19 vaccine and the potential impact of the vaccine in oncology clinical trials.

In conclusion, COVID-19 has placed a burden on health systems around the world. Unfortunately, there are still no promising guidelines for conducting clinical trials involving cancer patients during the COVID-19 pandemic. Furthermore, many unknown factors could hamper the results of clinical trials, which need to be studied. Due to the COVID-19 pandemic, few preclinical and clinical data are available, but there will be greater efforts to establish a promising guideline for conducting oncology clinical trials during the COVID-19 pandemic. Therefore, we anticipate that the factors associated with the severity of COVID-19 that we explored in the present study could help establish proper guidance for oncology clinical trials.

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**Informed consent**

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Not applicable.

**Declaration of competing interest**

The authors declare no conflicts of interest in association with the present study.

**References**

- [1] G. Khan, M. Sheek-Hussein, A.R. Al Suwaidi, K. Idris, F.M. Abu-Zidan, Novel coronavirus pandemic: a global health threat, *Turk J Emerg Med* 20 (2) (2020) 55–62.
- [2] C. Liu, Y. Zhao, D. Okwan-Duodu, R. Basho, X. Cui, COVID-19 in cancer patients: risk, clinical features, and management, *Cancer Biol Med* 17 (3) (2020) 519–527.
- [3] M. Dai, D. Liu, M. Liu, F. Zhou, G. Li, Z. Chen, Z. Zhang, H. You, M. Wu, Q. Zheng, Y. Xiong, H. Xiong, C. Wang, C. Chen, F. Xiong, Y. Zhang, Y. Peng, S. Ge, B. Zhen, T. Yu, L. Wang, H. Wang, Y. Liu, Y. Chen, J. Mei, X. Gao, Z. Li, L. Gan, C. He, Z. Li, Y. Shi, Y. Qi, J. Yang, D.G. Tenen, L. Chai, L.A. Mucci, M. Santillana, H. Cai, Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak, *Canc. Discov.* 10 (6) (2020) 783–791.
- [4] Y. Xu, H. Liu, K. Hu, M. Wang, Clinical recommendations on lung cancer management during the COVID-19 pandemic, *Thorac Cancer* 11 (7) (2020) 2067–2074.
- [5] A. Sanyaolu, C. Okorie, A. Marinkovic, R. Patidar, K. Younis, P. Desai, Z. Hosein, I. Padda, J. Mangat, M. Altaf, Comorbidity and its impact on patients with COVID-19, *SN Compr Clin Med* (2020) 1–8.
- [6] S. Elezkturaj, S. Greuel, J. Ihlow, E.G. Michaelis, P. Bischoff, C.A. Kunze, B.V. Sinn, M. Gerhold, K. Hauptmann, B. Ingold-Heppner, F. Miller, H. Herbst, V.M. Corman, H. Martin, H. Radbruch, F.L. Heppner, D. Horst, Causes of death and comorbidities in hospitalized patients with COVID-19, *Sci. Rep.* 11 (1) (2021) 4263.
- [7] E. Zlotorynski, Defective mitochondria ignite the SASP, *Nat. Rev. Mol. Cell Biol.* 21 (4) (2020) 179.
- [8] F. Coperchini, L. Chiovato, L. Croce, F. Magri, M. Rotondi, The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system, *Cytokine Growth Factor Rev.* 53 (2020) 25–32.
- [9] M. Colombo, L. Mirandola, M. Chiriva-Internati, A. Basile, M. Locati, E. Lesma, R. Chiamonte, N. Platonova, Cancer cells exploit notch signaling to redefine a supportive cytokine milieu, *Front. Immunol.* 9 (2018) 1823.
- [10] A.M. Battram, M. Bachiller, B. Martin-Antonio, Senescence in the development and response to cancer with immunotherapy: a double-edged sword, *Int. J. Mol. Sci.* 21 (12) (2020).
- [11] Z. Wang, C. Shi, Cellular senescence is a promising target for chronic wounds: a comprehensive review, *Burns Trauma* 8 (2020) tkaa021.
- [12] L. Prata, I.G. Ovsyannikova, T. Tchkonja, J.L. Kirkland, Senescent cell clearance by the immune system: emerging therapeutic opportunities, *Semin. Immunol.* 40 (2018) 101275.
- [13] M. Mohiuddin, K. Kasahara, The emerging role of cellular senescence in complications of COVID-19, *Cancer Treat Res Commun* 28 (2021) 100399.
- [14] J. Nehme, M. Borghesan, S. Mackedenski, T.G. Bird, M. Demaria, Cellular senescence as a potential mediator of COVID-19 severity in the elderly, *Aging Cell* 19 (10) (2020), e13237.
- [15] A.J. Pietrobon, F.M.E. Teixeira, M.N. Sato, Immunosenescence and inflammaging: risk factors of severe COVID-19 in older people, *Front. Immunol.* 11 (2020) 579220.
- [16] K. Bukowski, M. Kciuk, R. Kontek, Mechanisms of multidrug resistance in cancer chemotherapy, *Int. J. Mol. Sci.* 21 (9) (2020).
- [17] H.C. Zheng, The molecular mechanisms of chemoresistance in cancers, *Oncotarget* 8 (35) (2017) 59950–59964.
- [18] K. Gupta, S. Gandhi, A. Mebane 3rd, A. Singh, N. Vishnuvardhan, E. Patel, Cancer patients and COVID-19: mortality, serious complications, biomarkers, and ways forward, *Cancer Treat Res Commun* 26 (2021) 100285.
- [19] E. Moujaess, H.R. Kourie, M. Ghosn, Cancer patients and research during COVID-19 pandemic: a systematic review of current evidence, *Crit. Rev. Oncol. Hematol.* 150 (2020) 102972.
- [20] V.M. Martin Gimenez, F. Inerra, C.D. Tajer, J. Mariani, L. Ferder, R.J. Reiter, W. Manucha, Lungs as target of COVID-19 infection: protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment, *Life Sci.* 254 (2020) 117808.
- [21] M. Bansal, Cardiovascular disease and COVID-19, *Diabetes Metab Syndr* 14 (3) (2020) 247–250.
- [22] A.N. Kochi, A.P. Tagliari, G.B. Forleo, G.M. Fassini, C. Tondo, Cardiac and arrhythmic complications in patients with COVID-19, *J. Cardiovasc. Electro-physiol.* 31 (5) (2020) 1003–1008.
- [23] B. Long, W.J. Brady, A. Koyfman, M. Gottlieb, Cardiovascular complications in COVID-19, *Am. J. Emerg. Med.* 38 (7) (2020) 1504–1507.
- [24] S.R. Bornstein, F. Rubino, K. Khunti, G. Mingrone, D. Hopkins, A.L. Birkenfeld, B. Boehm, S. Amiel, R.I. Holt, J.S. Skyler, J.H. DeVries, E. Renard, R.H. Eckel, P. Zimmet, K.G. Alberti, J. Vidal, B. Geloneze, J.C. Chan, L. Ji, B. Ludwig, Practical recommendations for the management of diabetes in patients with COVID-19, *Lancet Diabetes Endocrinol* 8 (6) (2020) 546–550.
- [25] M.B. Ruiz-Roso, C. Knott-Torcal, D.C. Matilla-Escalante, A. Garcimartin, M. A. Sampedro-Nunez, A. Davalos, M. Marazuela, COVID-19 lockdown and changes of the dietary pattern and physical activity habits in a cohort of patients with type 2 diabetes mellitus, *Nutrients* 12 (8) (2020).
- [26] A. Rajpal, L. Rahimi, F. Ismail-Beigi, Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes, *J. Diabetes* 12 (12) (2020) 895–908.
- [27] M. Arruebo, N. Vilaboa, B. Saez-Gutierrez, J. Lambea, A. Tres, M. Valladares, A. Gonzalez-Fernandez, Assessment of the evolution of cancer treatment therapies, *Cancers* 3 (3) (2011) 3279–3330.
- [28] V.J. Costela-Ruiz, R. Illescas-Montes, J.M. Puerta-Puerta, C. Ruiz, L. Melguizo-Rodriguez, SARS-CoV-2 infection: the role of cytokines in COVID-19 disease, *Cytokine Growth Factor Rev.* 54 (2020) 62–75.
- [29] Y. Chi, Y. Ge, B. Wu, W. Zhang, T. Wu, T. Wen, J. Liu, X. Guo, C. Huang, Y. Jiao, F. Zhu, B. Zhu, L. Cui, Serum cytokine and chemokine profile in relation to the severity of coronavirus disease 2019 in China, *J. Infect. Dis.* 222 (5) (2020) 746–754.
- [30] Z.S. Xu, T. Shu, L. Kang, D. Wu, X. Zhou, B.W. Liao, X.L. Sun, X. Zhou, Y.Y. Wang, Temporal profiling of plasma cytokines, chemokines and growth factors from mild, severe and fatal COVID-19 patients, *Signal Transduct Target Ther* 5 (1) (2020) 100.
- [31] J.M. Zhang, J. An, Cytokines, inflammation, and pain, *Int. Anesthesiol. Clin.* 45 (2) (2007) 27–37.

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