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Original Research

Developing a risk assessment score for patients with cancer during the coronavirus disease 2019 pandemic



Alice Indini ^{a,*}, Erika Rijavec ^a, Michele Ghidini ^a, Monica Cattaneo ^{a,b},
Francesco Grossi ^a

^a Medical Oncology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

^b Department of Medicine (DAME), University of Udine, Udine, Italy

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Abstract The novel coronavirus (CoV) pandemic is a serious threat for patients with cancer, who have an immunocompromised status and are considered at high risk of infections. Data on the novel CoV respiratory disease (coronavirus disease 2019 [COVID-19]) in patients with cancer are still limited. Unlike other common viruses, CoVs have not been shown to cause a more severe disease in immunocompromised subjects. Along with direct viral pathogenicity, in some individuals, CoV infection triggers an uncontrolled aberrant inflammatory response, leading to lung tissue damage. In patients with cancer treated with immunotherapy (e.g. immune checkpoint inhibitors), COVID-19 may therefore represent a serious threat. After a thorough review of the literature on CoV pathogenesis and cancer, we selected several shared features to define which patients can be considered at higher risk of COVID-19. We combined these clinical and laboratory variables, with the aim of developing a score to weight the risk of COVID-19 in patients with cancer.

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Worldwide health services are facing the challenge of the novel coronavirus (CoV) disease (coronavirus disease 2019 [COVID-19]) pandemic [1], which is widely spreading rapidly and severely. Some categories of patients, including patients with cancer, are considered more at risk than others. Cancer itself develops in an immunocompromised field, supporting the evidence that

* Corresponding author: Medical Oncology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122, Milano, Italy. Fax: +39 0255032659

E-mail addresses: alice.indini@gmail.com, alice.indini@policlinico.mi.it (A. Indini).

oncology patients are more at risk of infections, and this risk is further increased by certain oncologic treatments (e.g. chemotherapy, radiotherapy [RT]). Medical oncologists have arranged their daily clinical practice in view of the current emergency, through the implementation of protective measures [2]. To date, no evidence-based recommendations have been provided owing to limited data of COVID-19 in oncology patients. Evidence from small case series suggest that COVID-19 diffusion in patients with cancer is not prominent as expected [3–6]. Rather, other comorbidities (e.g. cardiovascular disease, diabetes, chronic obstructive pulmonary disease) correlate with a higher risk of infection and severe events [7].

Owing to the peculiar pathogenesis of CoV in humans and to the mechanisms of action of novel oncologic treatments, the link between CoV and patients with cancer might not be straightforward. Unlike other common viruses, CoVs have not been shown to cause a more severe disease in immunocompromised subjects [7]. Along with a direct viral pathogenicity, the host's immune response plays a crucial role in COVID-19. In some individuals, CoV infection triggers an uncontrolled aberrant inflammatory response to external factors, which leads to lung tissue damage [8]. Since the introduction of anticancer immunotherapy (e.g. immune checkpoint inhibitors [ICIs]), most oncology patients have changed their features of immunocompromised

subjects. Rather, their immune system is somehow 'boosted' by the cancer treatment they receive. This might translate into a distinct susceptibility of these subjects towards CoV infections. The cross-interference of CoV and ICIs may worsen the clinical course of COVID-19, which, in turn, may intensify ICI-related side-effects [9]. Altogether, this evidence suggests that in patients treated with immunotherapy, COVID-19 (e.g. ICIs) may represent a serious threat [8].

The present article focuses on developing a score to weight the risk of COVID-19 in patients with cancer. The main issue raised by the pandemic is whether the risk of COVID-19 outweighs that of cancer treatment delay. In the present situation, oncologists need to decide which kind of patient should start (or continue) which kind of treatment and how much will this increase the risk of complications in case of COVID-19 [10]. After a thorough review of the literature on CoV pathogenesis and cancer, several shared features have been selected to define which patients can be considered at higher risk of complications in case of COVID-19.

The score includes clinical and laboratory variables, as indicated in Table 1. Regarding the patient's characteristics, all recognised risk factors for COVID-19 were included: older age, presence of comorbidities, obesity and sex [7]. Two more variables were included: performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale and

Table 1

The 'Milano Policlinico ONCOVID Score' for risk evaluation in oncology during the COVID-19 pandemic.

Variables	Score	Categories of risk for patients and for treatment delays during COVID-19 diffusion	
Patient characteristics			
Sex	F = 0 M = 1	<p>Score < 4: low risk</p> <ul style="list-style-type: none"> • Maintain treatment schedule. • Consider treatment delay in the presence of additional risk factors (e.g. comorbidities^a) or to reduce hospital access. • Consider telemedicine to monitor patients receiving an outpatient-basis treatment (e.g. oral anticancer drugs, HT). <p>Score 4–6: intermediate risk</p> <ul style="list-style-type: none"> • Consider treatment delays (e.g. modification of treatment schedules) for patients with partial response to treatment. • Consider treatment holidays for patients treated with IT or CT + IT for ≥6 months and/or with complete response to treatment. • Carefully monitor patients with history of irAEs. <p>Score ≥7: high risk</p> <ul style="list-style-type: none"> • Patients need to be frequently monitored for symptoms, also with the aid of telemedicine. • Variations in laboratory values may indicate subclinical changes. • Maintain treatment schedules only if safe administration is guaranteed; tailor treatment administration depending on the type of treatment and disease response. • Avoid unnecessary procedures (e.g. radiologic examinations) to reduce hospital access. 	
ECOG PS	0–1 = 0 ≥2 = 1		
Age	<70 = 0 ≥70 = 1		
BMI	<30 = 0 ≥30 = 1		
Comorbidities ^a	No = 0 Yes = 1 Yes >1 = 2		
Concomitant steroid treatment ^b	No = 0 Yes = 1		
Disease characteristics			
Thoracic tumour	No = 0 Yes = 1		
History of thoracic RT ^c	No = 0 Yes = 1		
Treatment characteristics			
Line of treatment	Adjuvant = 0 ≥1 = 1		
Type of treatment	HT/TKIs/TT/mAb = 0 CT = 1 IT/IT + CT = 2		

Table 1 (continued)

Variables	Score	Categories of risk for patients and for treatment delays during COVID-19 diffusion
History of irAEs ^d	No = 0 Yes = 1 Yes, pneumonitis = 2	
Laboratory values		
NLR	<5 = 0 ≥5 = 1	
LDH	<ULN = 0 ≥ULN = 1	
CRP	<ULN = 0 ≥ULN = 1	

BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; F, female; HT, hormonal therapy; irAEs, immune-related adverse events; IT, immunotherapy; LDH, lactate dehydrogenase; M, male; mAb, monoclonal antibody; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; RT, radiotherapy; TKIs, tyrosine kinase inhibitors; TT, targeted therapy; ULN, upper limit of normal.

^a Comorbidities include hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease and chronic systemic infections.

^b Concomitant steroid treatment includes continuous therapy with a dose of >10 mg daily of prednisone equivalent, lasting for more than the 1-month period.

^c Only for patients with extrathoracic tumours.

^d Only for patients treated with IT or IT + CT.

corticosteroid treatment. ECOG PS is a recognised risk factor for outcomes, and the presence of poor ECOG PS (i.e. ≥ 2) has been confirmed to be detrimental in patients with cancer and COVID-19 [6]. Long-lasting treatment with high-dose corticosteroids, commonly used as supportive therapy for patients with cancer and potentially associated with an increased risk of opportunistic infections, seems to have a negative impact on the COVID-19 outcome [5].

Regarding the underlying tumour characteristics, limited available data suggest that lung cancer diagnosis and ongoing thoracic RT at the time of the COVID-19 onset were common features of patients with severe disease [3–6]. In our score, these two items are meant to be included only once for patients with lung tumours. In fact, thoracic RT is commonly used as treatment for patients with lung tumours; however, this does not seem to further increase the risk according to available data. Nonetheless, patients with extrathoracic tumours receiving thoracic RT (e.g. for palliative treatment of metastases) should be considered at risk owing to the potential radiation damage to the lung tissue.

Considering all the aforementioned issues, the type and intent of oncologic treatment might have an impact on the risk of COVID-19 complications. The therapeutic setting (i.e. adjuvant versus treatment for metastatic disease) has an impact owing to differences in tumour burden and patients' general conditions. Immunotherapy or the combination of immunotherapy and chemotherapy is considered high-risk treatments, followed by chemotherapy and other anticancer drugs (e.g. hormonal therapy, targeted agents). Among patients receiving immunotherapy, those with a history of immune-related adverse events (irAEs) and/or disease response to treatment might be even more at risk. There is plenty of evidence that irAEs correlate with a

higher efficacy of immunotherapy, suggesting that an adequate immune response harms both the tumour and the host [11].

Common laboratory findings of patients with severe COVID-19 are lymphopenia, high neutrophil-to-lymphocyte ratio (NLR), high levels of inflammatory markers (e.g. C-reactive protein) and lactate dehydrogenase [1]. Polarisation of the immune response towards a proinflammatory profile also correlates with lower efficacy of immunotherapy and tumour progression, and baseline NLR correlates with survival outcomes and response to immunotherapy.

Altogether, these variables can be used to group oncology patients in distinct classes of risk in the actual COVID-19 emergency. The purpose of risk assessment is to help clinicians in treatment decisions. Given the lack of data in this field and the absence of a validation in the clinical setting, the assumption of a precise role of these variables is only conceptual. Prospective data collection is needed to translate these observations in clinical practice, with the aim of guiding risk-to-benefit considerations and treatment decision in specific subgroups of patients. Customisation of cancer treatment should be pursued, to provide patients with the best care in this critical situation.

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F.G. reports a consulting or advisory role for MSD Oncology, Bristol-Myers Squibb, AstraZeneca, Roche,

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References

- [1] Guan W, Ni Z, Liang W, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. <https://doi.org/10.1056/NEJMoa2002032>.
- [2] Indini A, Aschele C, Cavanna L, et al. Reorganisation of medical oncology departments during the novel coronavirus disease-19 pandemic: a nationwide Italian survey. *Eur J Canc* 2020;132:17–23.
- [3] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21(3):335–7.
- [4] Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020;21(4):e181.
- [5] Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020. <https://doi.org/10.1016/j.annonc.2020.03.296>.
- [6] Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in wuhan, China. *JAMA Oncol* 2020. <https://doi.org/10.1001/jamaoncol.2020.0980>.
- [7] Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY)* 2020 Apr 8:12. <https://doi.org/10.18632/aging.103000>.
- [8] Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020;38:1–9.
- [9] Di Giacomo AM, Gambale E, Monterisi S, et al. SARS-COV-2 infection in cancer patients undergoing checkpoint blockade: clinical course and outcome. *Eur J Canc* 2020. <https://doi.org/10.1016/j.ejca.2020.04.026>.
- [10] Hanna TP, Evans GE, Booth CM. Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. *Nat Rev Clin Oncol* 2020. <https://doi.org/10.1038/s41571-020-0362-6>.
- [11] Indini A, Di Guardo L, Cimminiello C, et al. Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma. *J Canc Res Clin Oncol* 2019;145(2):511–21.