Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Cancer population may be paradoxically protected from severe manifestations of COVID-19 ☆

Dear Editor,

We read with great interest the meta-analysis by Afshar and colleagues regarding the very high case-fatality rate in cancer patients infected with SARS-CoV-2.[1] The authors suggest that such findings can be explained by the "systemic immunosuppression" because of cancer and its associated treatments.[1] The official death toll of the COVID-19 pandemic has reached, as of May 27th, 350 000 and it is now recognised that severe outcomes of this infection are associated to a complex dysregulated immune response to SARS-CoV-2 which clinically translates into acute respiratory distress syndrome, the cytokine release syndrome, the secondary hemophagocytic lymphohistiocytosis, and the disseminated intravascular coagulation.[2] Large series from Wuhan, China have identified several risk factors for death in the COVID-19 population: for instance, Li and colleagues found at survival analysis that male sex, older age, leukocytosis, high lactate dehydrogenase level, cardiac injury, hyperglycemia, and the use of systemic steroids were all significant predictors.[3] In such early reports, cancer patients who were infected with this novel coronavirus were considered to have an incredibly high mortality rate (almost 30%).[4] However, these data were subsequently criticised because of several methodological issues such as the many non-cancer comorbidities or other confounding factors that were not controlled in the analysis of the cohort; in addition, a clear definition of some of the variables (e.g., cancer type or stage) was not always fully specified.[5] On the contrary, other authors have subsequently suggested that cancer patients, because of their impaired immune system due to the tumor itself and its therapies, are expected to have *a reduced* systemic inflammatory response to the virus and, thus, non-inferior mortality rates.[6]

In the face of these conflicting results, more data are needed. We therefore reviewed the medical records of all the 119 patients with a confirmed COVID-19 admitted to the Department of Infectious and Tropical Diseases of Careggi University Hospital, Florence from February 29 to April 11, 2020. Calculations were performed using SPSS for Windows (v.21, SPSS Inc., Armonk, NY, USA). Among them, 18 (15.1%) patients reported a history of cancer (2 prostate, 2 breast, 2 multiple myeloma, 2 colon, 2 lymphomas, 1 leukemia, 2 larynx, 1 urothelial, 1 thyroid, 2 renal, 1 pancreas). According to the clinical course and despite a significantly older group and a higher proportion of former smokers, admission to the Intensive Care Unit (ICU) was documented only in 3 cancer cases with no difference when compared to the non-cancer population (Table 1). Overall, 33.3% in the cancer group died from COVID-19, while among non-cancer patients, fatal evolution was reported in a lower yet statistically not significant rate (13.9%; $p = 0.289$). By univariate logistic regression analysis, cancer patients seem to have an increased risk of death (OR=4.77, $p = 0.013$). However, when performing multivariate analysis accounting for age, smoking status, and cardiovascular disease, the result is no longer significant (Table 2). Looking at laboratory parameters, white blood cell count and several inflammatory markers were recorded on admission (ie, before beginning any possibly modifying treatment such as steroids or anti-IL6 drugs). Interestingly, no significant differences were found in terms of the mean concentration of the most important cytokines between the two groups.

It is assumed that the development of cancer is associated with a blunted immune-status characterized by an altered production of cytokines, an impaired dendritic cell activation, and a dysfunctional lymphocyte population; such impairment is also enhanced by the unavoidable surgical and non-surgical treatments.[7] On the contrary, COVID-19 patients with adverse clinical outcomes usually show an aggressive inflammatory response, and the levels of IL-6 were recently shown to be directly associated with the risk of adverse outcomes.[8]

Overall, our findings seem to confirm the role of age as one of the strongest prognostic factors; in addition, we suggest that cancer patients are not necessarily at higher risk for COVID-19 associated death because their impaired immune responsiveness might act as a protective factor from the cytokine storm.[5] This apparently paradoxical situation in the immune impaired populations that have a higher risk to be infected but a higher probability of a benign clinical course was also recently reported for a cohort of patients under immunosuppressive treatment because of several rheumatological disorders.[9] Even in the case of HIV-SARS-CoV-2 coinfection, the preliminary results seem to confirm that the prognosis is not worse than the general population.[10] While waiting for more robust evidence, a feared worse outcome for cancer patients affected by COVID-19 appears, at the moment, not justified. Our analysis was also the first, to the best of our knowledge, to directly compared COVID-19 cancer and non-cancer patients from both a clinical and immunological point of view. However, it does suffer from some limitations that are in common with the aforementioned studies: the cancer type and clinical/pathological stage, and the type and time elapsed since the last treatment should be separately evaluated. Reasonably, only future studies in larger cohorts accounting for all the complex interactions between the host response to this novel coronavirus and the consequences of cancer and its treatment on the immune system will solve this issue.

☆ Short Summary: "Cancer patients infected with COVID-19 have not a significantly different clinical prognosis"

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Table 1
A descriptive cohort of the COVID-19 patients and stratified by the presence of a history of cancer. Chi-squared test or two-tailed Student's *t*-test were used to explore the differences.

	Cancer patients ($n = 18$)	Non-cancer patients ($n = 101$)	*p*-value
Median age, years	73.7	64.2	0.018
Male sex	12 (66.7)	61 (60.4)	0.708
Smoking Status			0.034
- Never	9 (50)	53 (52.5)	
- Current	0 (0)	8 (7.9)	
- Former	7 (38.9)	25 (24.8)	
- Unknown	2 (11.1)	15 (14.8)	
Comorbidities			
- Hypertension	6 (33.3)	28 (27.7)	0.340
- Chronic Heart Disease	2 (11.1)	13 (15.8)	0.315
- Diabetes Mellitus	1 (5.6)	16 (15.8)	0.514
- Chronic pulmonary disease	2 (11.1)	13 (12.9)	0.412
- Chronic Kidney Disease	4 (22.2)	4 (3.9)	0.529
- Chronic Liver Disease	1 (5.6%)	1 (0.9)	0.941
Signs and symptoms at on admission			
- Fever	14 (77.8)	93 (92.1)	0.082
- Cough	7 (38.9)	65 (64.3)	0.057
- Pharyngeal pain	1 (5.6)	4 (3.9)	0.322
- dyspnea	10 (55.6)	30 (29.7)	0.162
- Fatigue	4 (22.2)	19 (18.8)	0.648
- Myalgia	1 (5.6)	9 (8.9)	0.602
- diarrhea	2 (11.1)	19 (18.8)	0.704
- Nausea and/or vomiting	1 (5.6)	8 (7.9)	0.251
- Nasal congestion	0 (0)	5 (4.9)	0.644
- Headache	0 (0)	7 (6.9)	0.535
Severe course			
- Transfer to Intensive Care Unit	3 (11.1)	19 (18.1)	0.344
- Death	6 (33.3)	14 (13.9)	0.289
- Need for Intubation	0 (0)	7 (6.9)	0.623
Inflammatory Markers on Admission, mean (±SD)			
- WBC ($x10^9$/L)	7.4 (±4.4)	6.6 (±3.6)	0.459
- IL-1beta (pg/mL)	1.2 (±0.9)	1.0 (±1.1)	0.349
- IL-6 (pg/mL)	37.5 (±62.8)	27.5 (±46.8)	0.455
- IL-8 (pg/mL)	33.2 (±24.6)	72.6 (±159.5)	0.806

Table 2
Factors predictive of death in hospitalised patients with COVID-19 by univariate and multivariate logistic regression model.

Covariates	Univariate Analysis			Multivariate Analysis		
	Beta *(standard error)*	OR *(CI 95%, Wald)*	p-value	Beta *(standard error)*	OR *(CI 95%, Wald)*	p-value
Age	0.021 *(0.011)*	1.021 *0.999 - 1.045*	0.063	0.096 *(0.031)*	1.101 (*1.035 - 1.170*)	0.002
Smoke habit	1.472 *(0.561)*	4.359 *(1.452 - 13.091)*	0.009	0.990 *(0.691)*	2.692 *(0.696 - 10.420)*	0.152
Cardiovascular Diseases	2.221 *(0.786)*	9.214 *(1.973 - 43.041)*	0.005	1.054 *(0.877)*	2.870 (0.514 - *16.008*)	0.229
Cancer	1.563 *(0.630)*	4.773 *(1.388 - 16.406)*	0.013	0.764 *(0.782)*	2.147 (***0.463 - 9.947***)	0.329

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent: Informed consent was obtained from all individual participants included in the study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

All authors declare they have nothing to disclose.

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