



## Spotlight

## Why the complications of COVID-19 patients differ in elderly and young cancer patients

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## ABSTRACT

Zhang et al. reported the impact of different risk factors and comorbidities in COVID-19 lethality. The authors observed that the odds of dying by COVID-19 in cancer patients decrease with age and cancer becomes a non-significant factor above 80 years. We speculate on the possible causes for the different COVID-19 severity between elderly and young patients. Several factors that can have a different impact on young and elderly have to be taken into account such as inflammation, microbiota and anti-cancer therapies. Inflammation is a complex process that characterizes elderly people and it is believed to contribute to the severity of COVID-19 associated with old age. Cancer and related therapies may alter the process of inflammation both quantitatively and qualitatively and could impact on COVID-19 severity. Moreover, therapies used in elderly cancer patients are usually different from that used for young people where the presence of comorbidities and the mechanisms of action of the different drugs both on the susceptibility genes and on other factors have to be considered. Sex hormones and anti-estrogen therapies affect significantly gene expression in target cells thereby modulating the susceptibility of the tissues to SARS-CoV-2 infection and as a consequence the extent of the symptoms. The concentration of sex hormones varies with aging and among sexes. Interestingly, recent evidences, further corroborate the hypothesis that also sex hormones or anti-estrogen therapies impact the susceptibility to COVID-19 and its severity.

## Dear Editors

We read with great interest the manuscript by Zhang et al. that reported on the impact of different risk factors and comorbidities in the death by Coronavirus disease 2019 [1]. We congratulate the authors for the very interesting paper and the intriguing results. In particular, our attention was captured by the impact of cancer as a risk factor for death by COVID-19 in relation to aging. Counterintuitively, the odds of dying by COVID-19 in cancer bearing patients decreases with age (OR=31.538 [95% CI 5.213–158.787],  $p < 0.001$ , age < 40 years old) (OR=2.395 [95% CI 1.456–3.744],  $p < 0.001$ , age 40–60 years old) (OR=1.771 [95% CI 1.345–2.301],  $p < 0.001$ , age 60–80 years old) and cancer becomes a non significant factor above 80 years [1]. It is tempting to speculate about the causes behind this observation. Inflammation is a complex process that characterizes elderly people and it is believed to contribute to the severity of COVID-19 associated with old age. However, cancer

patients do not behave as expected and having cancer becomes an irrelevant feature with respect to dying of COVID-19 in people above 80 years old. This observation suggests that inflammation may play a different role or be influenced in its extent and quality by cancer or by specific therapies in the elderly. On the other hand, having cancer modifies the immune cells in terms of quality and of quantity. The microbiota is also different in young and elderly and can affect the severity of COVID-19 as it does the presence of other viruses such as HPV, HSV and EBV influencing the general conditions of the patients. Aging involves not only epithelial cells but also macrophages and inflammatory cells that are clearly involved in the manifestation of COVID-19 severe symptoms [2,3]. The authors report that elderly patients are characterized by a greater prevalence of leukocytosis, lymphopenia, decreased platelet count, hemoglobinemia, lower albumin, increased D-dimer, and prolonged prothrombin times which may contribute to the severity of the disease. Moreover, elderly males show a

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chronic upregulation of IL-6 and its elevation also predicts mortality due to COVID-19 [1] and causes a strong inflammatory response. However, our understanding of the factors associated with those features is still limited and requires deeper investigation. Interestingly, the situation is different in centenarians who are characterized by anti-inflammatory markers and specific longevity traits which seem to protect them from poor outcomes. The presence of protective factors from COVID-19 mortality in centenarians has been recently observed also by the Robert Koch Institute who reports a mortality rate of 46.7% by COVID-19 for German SARS-CoV-2-infected patients aged 80–89 while 23.3% only for people above 90 and up to 117 years old [4]. This intriguing observation should be better explored in a wider cohort of centenarians in order to understand the mechanism or the features associated with a lower severity and mortality rate for COVID-19 in this subset of individuals. An interesting link between extreme longevity and IL-6 signaling was described by Zeng et al. [5], who found that the IL-6 gene polymorphism SNP rs2069837 is significantly associated with centenarians that were shown to overexpress anti-inflammatory variants in immune/inflammatory genes [6]. In addition, other factors such as the tissue localization and the level of expression of COVID-19 susceptibility genes (ACE2, TMPRSS2 and NRP1), which are differently expressed in females and males, and in young and old individuals [7–9], can contribute to the diverse severity of the disease. An explanation could be that a lower expression of the susceptibility genes in normal tissues in the elderly population as compared to young individuals prevents synergism between cancer and COVID-19 while cancer in a young person may be associated with a worsening in the odds ratio of dying of COVID-19 due to the context in which SARS-CoV-2 infection and tissue tropism is manifested. According to this hypothesis, our data confirm that ACE2 and TMPRSS2 are expressed to a lower level in the tissues from the elderly as compared to young people [10].

In addition, it should be considered that different types of cancer affect young and old individuals therefore the synergy with COVID-19 and the following symptomatology may be influenced by that as well.

Moreover, the therapy used in elderly cancer patients may be different from that of young people due to the presence of comorbidities and fragilities in the elderly as well as the underlying mechanisms of action of the different drugs both on the susceptibility genes and on other factors that also affect the differences observed in young and elderly cancer patients. Sex hormones and anti-estrogen therapies, for example, affect significantly gene expression in target cells thereby modulating the susceptibility of the tissues to SARS-CoV-2 infection and as a consequence the extent of the symptoms [11]. The concentration of sex hormones varies with aging, it is different between sexes and it is modulated during the menstrual cycle and pregnancy. Interestingly, recent evidences, further corroborate the hypothesis that also sex hormones or anti-estrogen therapies impact the susceptibility to COVID-19 and its severity [12].

#### Authors contributions

SB and MM conceived the idea, wrote the manuscript and provided a critical framework. FN, AG, CC, RM, LM, MZ, FP, MC, SR, MMT analyzed the studies in the literature. All authors proofread the manuscript, provided final approval to publish it and agreed to be accountable for all aspects of the manuscript.

#### Ethical approval

Not applicable.

#### Data availability statement

Not applicable.

#### 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.

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