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Commentary

# Gender differences in outcomes of cancer patients with COVID: Signal or noise?

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Cancer is the second leading cause of deaths globally, responsible for 1 out of every 6 deaths [1]. COVID-19 pandemic has already resulted in the death of nearly 0.8 million people worldwide in just seven months [2]. Combine the two, and we have one of the most lethal combinations of diseases in the history of mankind.

Patients with cancer do not have the luxury to stay in complete lockdown during the pandemic. They need continued access to cancer treatment, supportive care or palliative care and are at a risk of being exposed to coronavirus. They may also face more severe outcomes from COVID-19 compared to the rest of the population, although the extent of this detriment is not clear [3]. Thus, cancer patients are constantly having to make the tough choice during the pandemic of either foregoing cancer treatments or risking COVID-19 infection by continuing to be exposed to the hospital environment. This decision is shaped by various factors: the risk-benefit thresholds for each patient, local policy, treatment intent and its level of evidence, mode of therapy (oral versus parenteral), frequency of visits, the prevalence of COVID-19 in the population, age of the patient, etc. But should gender also be one of those factors affecting this decision?

An intriguing finding seen in multiple observational studies is that COVID-19 seems to preferentially have worse outcomes in males versus females [4]. Whether this relationship holds true for cancer patients as well, and if so, is the effect size large enough to change policy remain unanswered. The systematic review and meta-analysis accompanying this comment seems to fill that knowledge gap [5]. Park et al. show that the odd's ratio (OR) for experiencing a composite endpoint including severe illness and all-cause death was 1.6(95% CI 1.38−1.85) in males versus females [5]. For severe illness and mortality separately, the OR was 1.47 (1.16−1.85) and 1.58 (1.18−2.13) respectively. Should these data change policy?

This meta-analysis has a fairly robust sample size combining 17 studies across the geographical regions and tumor types, including nearly 4000 patients. However, the definition of severe illness among the studies included in this meta-analysis was not uniform, some using ICU admission and some using clinical criteria. Since these outcomes are time-dependent, a hazard ratio would be a better metric than OR; this is not a limitation of the meta-analysis but of the included studies. Finally, the authors have described some rationale for why males and male cancers may be more susceptible to severe manifestations of COVID-19 such as seminal vesicles expressing receptors mediating the virus entry or the inflammation from virus in the vicinity affecting patients with prostate cancer [6]. A new research also suggests that differences in immune responses may explain this gender bias in COVID-19 outcomes. However, these bioplausibility explanations need to be taken with a grain of salt since they always succeed (not precede) observations.

The most important limitation of this study is that the associations are derived from univariate analyses of individual studies without adjusting for confounders. Only a few of the included studies reported multivariable adjusted OR, and the pooled OR for severe outcomes among these studies was 1.72 but with a wider confidence interval (1.09−2.71). Data from OpenSAFELY [4] and CCC19 registries [7] have identified age, the type of malignancy, the time of diagnosis, age, performance status, type of therapy, and comorbidities as factors increasing the risk of adverse outcomes with COVID-19 among patients with cancer. In this meta-analysis, we do not know the adjusted risk estimates when all these confounders have been accounted for. Furthermore, what constitutes "death due to COVID-19″ (death with versus death from) is not uniform across countries.

So, should these data change policy?

In our opinion, although important, this study should not lead to any panic among male patients with cancer or complacency among female patients with cancer. Whether male patients suffer more severe outcomes from COVID-19 still remains a hypothesis at this stage, waiting to be proven with robust big dataset studies that have adjusted for other variables we discuss above. The lack of absolute risk estimates and unmeasured confounders inherent to

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observational studies make these data only intriguing but not policy changing. Furthermore, even if males indeed had worse outcomes, the observed increase in odds are not convincing enough to change cancer treatment plans based on gender; the OR should not be mistaken for risk ratio. We also cannot prove causality- whether the adverse outcomes were due to COVID-19 or cancer or complications of cancer treatment. Indeed, male patients are known to have higher incidence and mortality due to cancer versus female patients, irrespective of COVID-19 [8,9]. Thus, at this point, similar precautionary principles to prevent the transmission of COVID-19 must be applied to cancer patients, irrespective of gender.

Beyond the immediate effect of severe illness and death caused by COVID-19 infection, gender disparities in long term outcomes will need further research. Women throughout the world experienced more economic and job insecurity and increased domestic workload as a result of the pandemic [10]. Women in LMIC are particularly vulnerable due to additional socioeconomic consequences such as lack of universal healthcare, domestic abuse and disruption of sexual and reproductive health [11]. These adverse socioeconomic determinants may affect women's access to cancer care not only during but also post-pandemic and affect cancer outcomes in the longer-term. As such, the ultimate effect of the pandemic on cancer outcomes by gender is yet to be determined.

Nonetheless, as academic researchers who are also practicing physicians, we are proud to see how clinicians and researchers have collaborated to create these databases at the time of increasing clinical workload due to the pandemic. These databases have helped us probe important questions, including looking for disparities in outcomes and access to treatments. Park et al. should be congratulated for integrating these rich data across different studies to address an important question regarding the role of gender in clinical outcomes for one of the most vulnerable subgroups: cancer patients with COVID-19. Their meta-analysis should lay the groundwork for future studies that should be designed specifically to answer the role of gender in cancer patients with COVID-19. At the time of a pandemic, every tidbit of information looks like a signal, and a false signal will distract. The medical community should remain vigilant and separate the wheat from the chaff with due diligence.

## Declaration of Competing Interest

None.

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## References

[1] World Health Organization. Fact Sheet on Cancer. Accessed athttps://www.who.int/news-room/fact-sheets/detail/cancer
[2] Our World in Data. Coronavirus (COVID-19) Deaths. Accessed athttps://ourworldindata.org/covid-deathson Aug 17, 2020.
[3] Robinson AG, Gyawali B, Evans G. COVID-19 and cancer: do we really know what we think we know? Nat Rev Clin Oncol 2020;17:386–8.
[4] Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020.
[5] Park R, Chidharla A, Mehta K, et al. Sex-bias in COVID-19-associated illness severity and mortality in cancer patients: a systematic review and meta-analysis. EClinicalMedicine 2020;26:100519.
[6] Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 2020. doi: 10.1038/s41586-020-2700-3. https://www.nature.com/articles/s41586-020-2700-3.
[7] Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. The Lancet 2020;395:1907–18.
[8] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA. A Cancer J Clin 2020;70:7–30.
[9] Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prevent 2011;20:1629–37.
[10] Burki T. The indirect impact of COVID-19 on women. The Lancet Infect Dis 2020;20:904–5.
[11] Wenham C, Smith J, Davies SE, et al. Women are most affected by pandemics - lessons from past outbreaks. Nature 2020;583:194–8.