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Research Paper

Sex-bias in COVID-19-associated illness severity and mortality in cancer patients: A systematic review and meta-analysis

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ABSTRACT

Background: Whether there is sex-bias within the adverse outcomes associated with COVID-19 in the cancer population is unknown. In this regard, several published studies have examined this question, but the results are inconclusive and inconsistent. To evaluate the sex-difference in the risk of adverse outcomes associated with COVID-19 in the cancer population, we have conducted a systematic review and meta-analysis.
Methods: Published articles evaluating adverse outcomes associated with COVID-19 in the cancer population from inception to June 2020 were identified by searching PubMed and EMBASE, ASCO 2020 Virtual Annual Conference, AACR 2020 COVID-19 and Cancer, ESMO conferences held from January to June 2020, and medRxiv and bioRxiv. Prospective or retrospective analyses in English, providing outcomes data with sex differences in the cancer population were included. The primary outcomes of interest were pooled ORs of severe illness, all-cause death, and the composite of severe illness and death attributable to COVID-19 in males versus females in cancer patients.
Findings: Overall, 3968 patients (17 studies) were analyzed in retrospective study settings. Overall, pooled ORs of the composite of severe illness and all-cause death in the setting of COVID-19 in males versus females was 1.60 (95% CI, 1.38−1.85). The risk of severe illness or death were both independently increased in males versus females.
Interpretation: Male sex was associated with a higher risk of severe illness and death attributable to COVID-19. This finding has implications in informing the clinical prognosis and decision making in the care of cancer patients.
Funding: This study received no funding.

1. Introduction

Early observational findings suggested that Coronavirus disease 2019 (COVID-19) is associated with disproportionately worse outcomes in males compared to females with subsequent studies providing statistical evidence for this clinical phenomenon and indicating that morbidity and mortality are higher in males despite no difference in the proportion of infected cases between the sexes [1,2]. As yet, the pathogenesis behind this sex-bias is not established, although a number of theories have been proposed. For example, an epidemiologic observation has been noted of the over-representation of androgenic alopecia in hospitalized male patients compared to their historical age-matched counterparts, suggesting the potential role of androgenic hormones in the pathogenesis [3]. Other studies suggest potential sex differences in one or more of the mult-step immunopathogenetic pathway including virus entry, innate immune virus recognition, and induction of adaptive immune response [4,5]. In addition, other epidemiological and clinical variables have emerged as risk factors for COVID-19 including age, comorbidities, and arguably, ethnicity [6-8]. Although the reason is unclear, nonetheless the epidemiological association of sex with adverse outcomes associated with COVID-19 appears to be established in the general community population.

Furthermore, a line of reasoning suggests a potential link between certain male-specific cancers and COVID-19 pathogenesis [9]. For example, seminal vesicles have been found to express ACE2 and TMPRSS2 which mediate severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) cellular entry and SARS-COV-2 has been

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Research in Context

Evidence before this study: Early observational findings had suggested that males have worse clinical outcomes compared females when afflicted with COVID-19 in the general healthy population. Whether there was sex-bias in clinical outcomes associated with COVID-19 in the cancer patient population has not been established. Previous studies had evaluated sex as a risk factor in the cancer population, however, results are conflicting and inconclusive.

Added value of this study: This systematic review and meta-analysis show that males compared to females in the cancer patient population have higher risk of severe illness as defined by illness requiring ICU admission and intubation and higher risk of all-cause death.

Implications of all the available evidence: These findings establish sex as a risk factor in the cancer patient population and suggest that it should be taken into account in the evaluation of COVID-19 risk in the oncology clinic setting.

detected in semen [10-13]. Although not well-established, inflammation as a result of SARS-COV-2 in the vicinity of the prostate may adversely impact patients with established prostate cancer while from the viewpoint of the infection, the male sex-organs may provide a viral reservoir to propagate infection.

The prevalence of cancer is estimated at 2% in patients with COVID-19 [14]. Furthermore, cancer patients comprise a population vulnerable to COVID-19 associated illness with strong evidence for higher risk of adverse outcomes compared to the general population [15]. Therefore, the development of strategies to minimize viral exposure is critical to oncologic care in the COVID-19 era. On the other hand, the ongoing care of cancer patients often cannot be delayed without causing harm [16]. Thus, the risk-benefit calculation of cancer patients in ongoing care must be precise and necessitates the accumulation of evidence. To this end, recent studies have analysed the COVID-19 associated sex-bias specifically within the cancer patient population in order to inform the clinical decision making in this patient population. However, the results are conflicting and inconclusive. Therefore, herein we have conducted a systematic review and meta-analysis to synthesize the evidence behind sex-bias within COVID-19 associated illness severity and death specifically within the cancer patient population.

2. Methods

2.1. Search strategy and inclusion criteria

The following study is not registered. Published articles that evaluated clinical outcomes associated with severe illness or death attributable to COVID-19 in the cancer patient population from inception to June 1, 2020 were identified by searching PubMed and EMBASE, as well as the ASCO 2020 Virtual Annual Conference, AACR 2020 COVID-19 and Cancer, ESMO conferences held from January 2020 to June 1, 2020, and the pre-print databases medRxiv and bioRxiv. The inclusion criteria consisted of the following: prospective or retrospective analyses, studies published in English, providing clinical outcomes

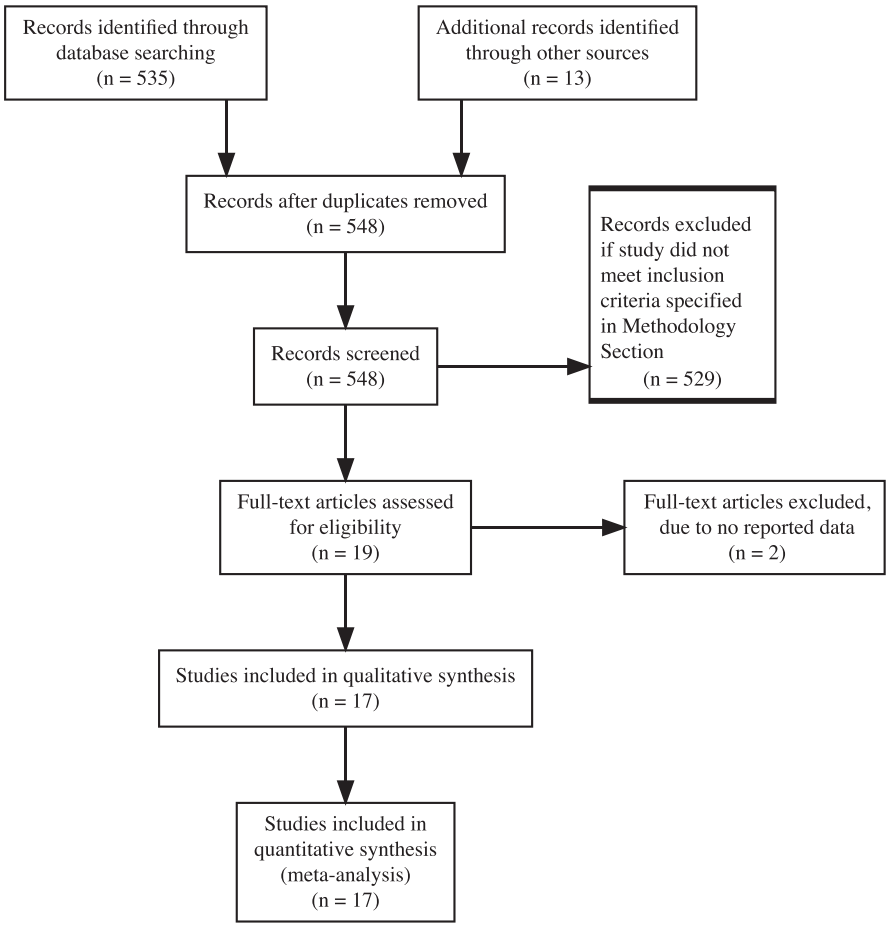

Fig. 1. Flow diagram.

Table 1
Characteristics of included studies.

Author	Country	Median age (range)	N	Most Common Cancer Types	Most Common Treatments Used	Outcome	Statistical Analysis Model for Reported Outcomes	Definition
Kuderer [18]	Multi-national (Spain, Canada, USA)	66 (57–76)	928	Hematological cancer (22%), Breast cancer (21%), Prostate cancer (16%)	Azithromycin + Hydroxychloroquine (20%)	Death Severe illness + death	Both bivariable unadjusted and multivariable adjusted ORs (age, smoking, obesity)	Requiring ICU admission or leading to death
Liang [19]	China	63 (47–87)	18	Lung cancer (28%), GI cancer (22%), Breast cancer (11%)	Not stated	Severe illness + death	No calculated OR data reported. Only raw data available.	Requiring ICU admission or leading to death
Tian [20]	China	64 (58–69)	232	Bladder cancer (14%), Breast cancer (13%), Colorectal cancer (11%)	Antibiotics (88%), Antiviral (79%), Immunomodulator (37%)	Severe illness	No calculated OR data reported. Only raw data available.	Any of the following: respiratory rate at least 30 per minute, oxygen saturation at most 93% in resting state, PF ratio less than 300, 50% lesion progression in lung imaging within 24–48 h
Yang [21]	China	63 (56–70)	205	Breast cancer (20%), Colorectal cancer (14%), Lung cancer (12%)	Antivirals (94%), Antibiotics (70%), Systemic steroids (30%)	Death	Both univariable unadjusted and multivariable adjusted ORs (receiving chemotherapy within 4 weeks before symptom onset, cancer type, time since cancer diagnosis)	n/a
Garassino [22]	Multi-national (European countries)	Recovered 67 (59–74) Died 70 (64–76) Ongoing 66.5 (59–74)	400	Lung cancer	NR	Severe illness + death	Both univariate unadjusted and multivariate adjuted OR (age, smoking status, hypertension, chronic obstructive pulmonary disease)	Requiring ICU admission or leading to death
Basse [23]	France	62 (52–72)	141	Breast cancer (40%), Hematological cancer (13%), Lung cancer (13%)	Antibiotics (48%), Steroids (5%), Hydroxychloroquine (4%)	Severe illness + death	Univariate unadjusted OR only	Requiring ICU admission or leading to death
Wang [24]	China	63 (55–70)	283	Lung cancer (18%), Breast cancer (13%), Colorectal cancer (12%)	Antiviral (93%), antibiotics (82%), immunoglobulins (40%)	Severe illness + death	Univariate unadjusted OR only	Requiring ICU admission or leading to death
Russell [25]	UK	67	106	Urogynecological cancer (34%), Hematological cancer (17%), Breast cancer (15%)	NR	Severe illness + death	Univariate unadjusted OR only	Requiring ICU admission or leading to death
Robilotti [26]	USA	No median age reported. Most over 60 years old.	423	Hematological cancer (24%), Breast cancer (20%), Colorectal cancer (9%)	Hydroxychloroquine (35%), Antibiotic (33%), Systemic steroids (28%)	Severe illness + death	Univariate unadjusted OR only	Requiring ICU admission or leading to death
Luo [27]	USA	68 (31–91)	102	Lung cancer	NR	Severe illness Death	Univariate OR of death or severe illness	Severe illness defined as ICU admission, intubation and mechanical ventilation, or transition to Do Not Intubate
Mehta [28]	USA	69 (10–92)	218	Hematological cancer (24%), Genitourinary cancer (21%), Breast cancer (12%)	NR	Severe illness Death	Univariate OR of death or severe illness	Severe illness defined as ICU admission and requiring mechanical ventilation
Stroppa [29]	Italy	71 (50–84)	25	Lung cancer (32%), GI cancer (24%), Genitourinary cancer (24%)	Antiviral (80%), Hydroxychloroquine (20%)	Death	Univariate OR of death	n/a

(*continued on next page*)

Table 1 (*Continued*)

Author	Country	Median age (range)	N	Most Common Cancer Types	Most Common Treatments Used	Outcome	Statistical Analysis Model for Reported Outcomes	Definition
Yarza [30]	Spain	66 (63–68)	63	Lung cancer (27%), Colorectal cancer (16%), Breast cancer (16%)	Lopinavir + Ritonavir + Hydroxychloroquine + Azithromycin (27%), Hydroxychloroquine + Azithromycin (67%)	Severe illness Death	Multivariate OR (adjusted by age, ECOG, metastasis, previous VTE, COPD) and 95% CI of death or severe illness	Severe illness defined as ARDS
Yu [31]	China	66 (48–78)	12	Lung cancer (58%), GI cancer (25%)	NR	Severe illness Death	Univariate OR of death or severe illness	Severe illness defined per The 2019 Novel Coronavirus (COVID-19) Diagnostic Criteria 5th edition
Zhang [32]	China	66 (37–98)	107	Lung cancer (19%), GI cancer (18%), Genitourinary cancer (18%)	Antivirals (92%), Steroid therapy (36%), immunoglobulins (20%)	Severe illness Death	Univariate OR of death or severe illness	Severe illness defined per WHO criteria
Dai [33]	China	64 (NR)	105	Lung cancer (20%), GI cancer (12%), Breast cancer 10%)	Antibiotics (77%), Antivirals (71%), Systemtic steroids (18%)	Severe illness Death	Univariate OR of death or severe illness	Severe illness defined as severe symptoms
Lee [34]	UK	69 (59–76)	800	Hematological cacncer (22%), GI cancer (19%), Breast (13%)	NR	Severe illness Death	Univariate OR and 95% CI Multivariate OR (adjusted by age, comorbidities) and 95% CI	Severe illness defined per WHO criteria

datawithsexdifferencesinthecancerpatientpopulation.Databasesearch and study selection was conducted by RP and AC then any discrepancies wereresolved*via*mediationbyAK.

2.2. Quality of studies and end points of interest

Study quality was assessed using the Newcastle Ottawa Scale for case-control studies. Quality score greater than or equal to seven on the Newcastle Ottawa Scale were deemed of high quality. The primary outcomes of interest were pooled odds ratios (OR) for death and the composite outcome of severe illness and death attributable to COVID-19 in males versus females.

2.3. Data extraction and statistical analysis

Author, date of publication, country, type of study, analysis model used (univariate versus multivariate), median and range of age, cancer types included in the study, definitions of severe illness, and the calculated ORs for severe illness and death attributable to COVID-19 were retrieved. In the analysis for the composite outcome of severe illness and mortality, reported OR of composite outcome was used, but where this was not available, OR of death or OR of severe illness was included. If calculated OR data was not available, raw data was used to calculate the OR in a univariate analysis model and included in the meta-analysis. Otherwise, OR derived from univariate analysis was included in the analysis as the majority of the studies did not report multivariate ORs.

Pooled ORs and 95% confidence intervals (CI) were calculated using a meta-analytical method that weighed the logarithm of the OR by the function of its variance for each study. Results derived from the random effects model were reported under the assumption of significant heterogeneity. Dersimonian-Laird Model was used to fit the random effects model. Subgroup analysis was performed with stratification by country of study origin and for studies reporting multivariate adjusted ORs. Publication bias was assessed using the Begg's funnel plot. Meta-analysis was performed using the package 'metafor' of the R-project.

2.4. Role of funding source

This study received no funding.

3. Results

3.1. Study characteristics and quality

Overall, 3968 patients (17 studies) were analyzed in retrospective study settings (Fig. 1). Of these studies two were conducted in multinational settings whereas the rest were conducted in China [10], France (1), United Kingdom (1), and United States (3). Median ages were similar across studies (range, 62–70). 10 studies reported outcomes for all-cause death, 10 studies for severe illness, and 2 studies for severe illness and death combined. Severe illness was defined as either illness requiring ICU admission or based on the WHO criteria for severe COVID-19 (Table 1).

3.2. Pooled analysis of severe disease, death, and composite outcome

Overall, pooled ORs of univariate analyses of the composite of severe illness, death, and severe illness or death was higher in males versus females (OR 1.60, 95% CI, 1.38–1.85). Heterogeneity was found to be low (I^2 = 4%). Furthermore, pooled ORs of univariate analyses for severe illness, death, or severe illness of death were all found to be higher in males versus females (severe illness, OR 1.47, 95% CI, 1.16–1.85; death, OR 1.58, 95% CI, 1.18–2.13; severe illness or death, OR 1.66, 95% CI, 1.02–2.71) (Fig. 2).

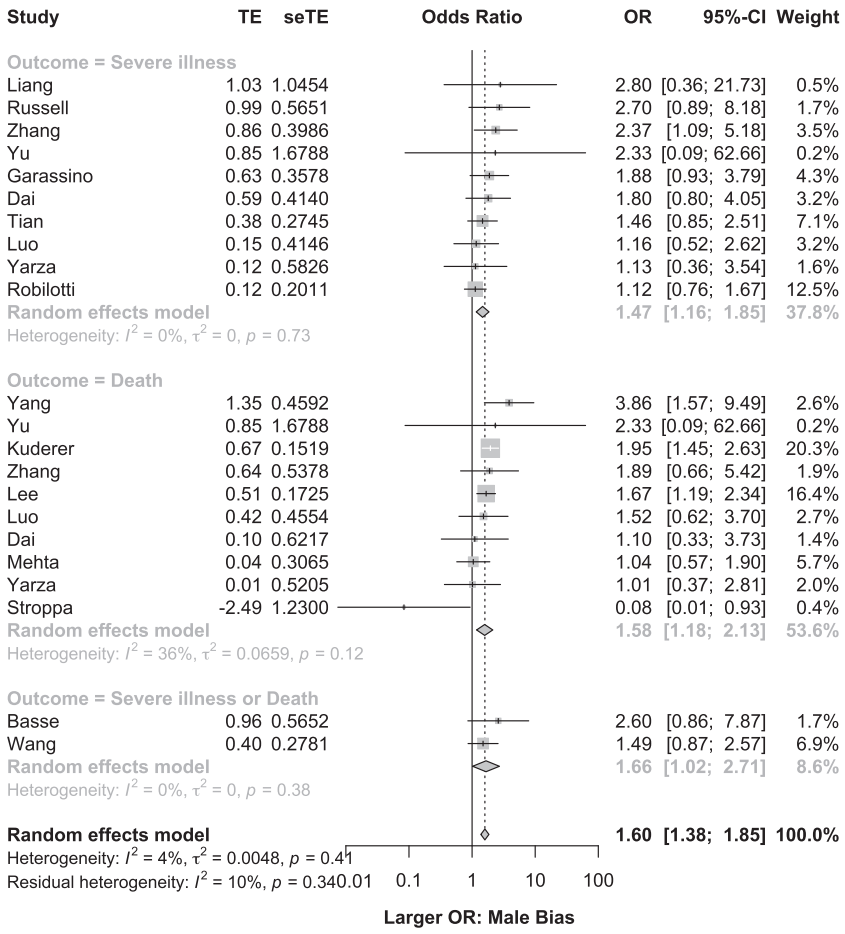

Fig. 2. Pooled odds ratios of severe illness, death, and composite outcome.

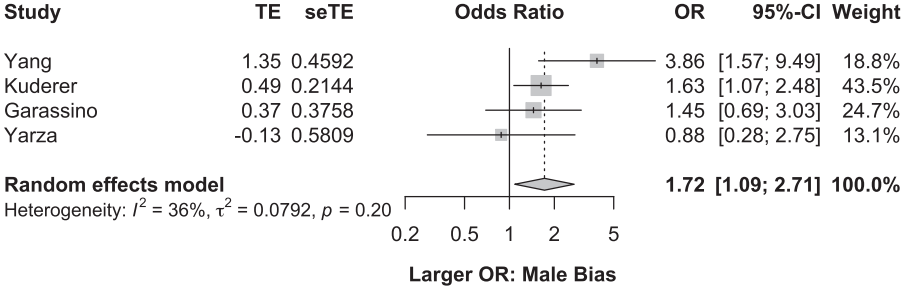

Fig. 3. Pooled multivariate odds ratios of death.

3.3. Subgroup analyses

Pooled OR of univariate analyses of death was still higher for males versus females regardless of country of study origin with no significant between-group differences were seen (China, 2.27 [1.26–4.09] vs. European or North American countries, 1.43 [1.00–2.03]; test for subgroup differences, p-value = 0.1834) (Supplemental Figure 1). Pooled OR of univariate analyses of severe illness was also higher for males versus females with no significant between-group differences between the location of study (China, OR 1.77 [1.21–2.58] vs. European or North American countries, OR 1.22 [0.88–1.68]; test for subgroup differences, p-value = 0.1834) (Supplemental Figure 2). Pooled ORs of multivariate analyses of death was still higher for males versus females consistent with the pooled univariate ORs (OR, 1.72, 95% CI, 1.09–2.71) (Fig. 3).

3.4. Publication bias

No significant between-study bias was detected per Begg's funnel plot (Fig. 4). All studies included in the meta-analysis were of high quality based on the Newcastle Ottawa Scale (Supplemental Table 1).

4. Discussion

This study has evaluated the association between sex and COVID-19-associated clinical outcomes in the cancer patient population. Furthermore, the generalizability of our results is supported by the included studies spanning multiple countries across several continents. Finally, our analysis reports multiple clinical outcome associations the results of which are all in agreement, strongly supporting the conclusion.

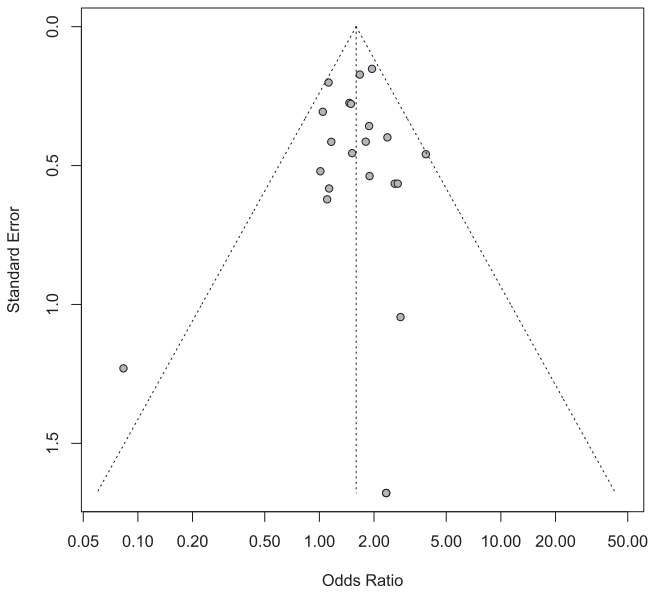

Fig. 4. Funnel plot.

A recent meta-analysis found that in the general community population, odds ratios of risk of death was 1.6 (95% CI, 1.54−1.71) in males compared to females (2). This result is comparable to our results (OR 1.58, 95% CI, 1.18−2.13), suggesting that the sex-bias for adverse outcomes is similar in the cancer patient population. Moreover, these results suggest that the mode in which biological sex affects the risk of adverse outcomes in COVID-19 is less likely to be modified cancer. Indeed, further mechanistic studies are warranted to arrive at the pathogenesis of COVID-19 with respect to the involvement of biological sex.

Given that all-cause death was the outcome of interest in this meta-analysis and given the advanced median age across studies, death due to non-COVID-19 causes including cancer itself is difficult to dissect as noted in other studies [17]. Possible reasons for this may be that cancer patients have inherently worse general health and that they may die 'with' rather than 'due to' COVID-19 or that there may be 'misattribution' of death. It is important that cancer and COVID-19 research be available in timely manner to those involved in oncological care as the management of this disease in the cancer population as well as the management of cancer in the COVID-19 era are rapidly developing. Nonetheless, it is equally important to not sacrifice meticulousness and soundness of scientific investigation for the sake of expediency despite the extraordinary times that the scientific community faces. Future outcomes studies should be mindful of this notion in investigations regarding outcomes in the setting of COVID-19 including for cancer patients.

Our study has a number of limitations. First, because the included studies were conducted in retrospective settings, the biases associated with such studies should be considered in interpreting the results of this meta-analysis. Furthermore, reported ORs derived from univariate analyses were used in the meta-analysis due to lack of reported multivariate adjusted ORs in included studies. However, sensitivity analysis showed that there was no significant difference between results reported from univariate and multivariate models. Second, pre-print databases were included in the meta-analysis despite their lack of peer review due to the rapidly evolving nature of COVID-19-related science and in order to increase our study's power in this unique setting. Furthermore, studies were scrutinized closely for quality using two separate scales prior to inclusion to control the quality of the meta-analysis. Third, there was overlap in the clinical outcomes evaluated. The definition of severe illness used in the included studies consisted of both ICU admission and death. For this reason, whether male sex was associated with severe illness excluding mortality remains unclear. Further studies are warranted to dissect this association.

In conclusion, the male sex appears to be a risk factor for severe illness and death due to COVID-19 in the cancer patient population. This finding may help guide the decision making in oncologic care and patient counselling in the clinic especially as societies move towards re-opening and towards a new-normal.

Author contributions

Conceptualization, A.K; validation, R.P, A.C, A.K..; investigation, R. P, A.C., A.K.; writing—original draft preparation, R.P., A.K.; writing—review and editing, R.P., A.C., K.M., W.S., E.W, A.K.; supervision, A.K.; project administration, A.K.; All authors have read and agreed to the published version of the manuscript.

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Data sharing statement

The authors report no additional datasets to be shared other than that reported in the manuscript.

Declaration of Competing Interest

The authors report no conflicts of interest pertaining to this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2020.100519.

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