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ORIGINAL ARTICLE



# Association of active oncologic treatment and risk of death in cancer patients with COVID-19: a systematic review and meta-analysis of patient data

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**ABSTRACT**

**Background:** Cancer patients suffer from worse coronavirus disease-2019 (COVID-19) outcomes. Whether active oncologic treatment is an additional risk factor in this population remains unclear. Therefore, here we have conducted a systematic review and meta-analysis to summarize the existing evidence for the effect of active oncologic treatment on COVID-19 outcomes.

**Methods:** Systematic search of databases (PubMed, Embase) was conducted for studies published from inception to July 1, 2020, with a subsequent search update conducted on 10 October 2020. In addition, abstracts and presentations from major conference proceedings (ASCO, ESMO, AACR) as well as pre-print databases (medxriv, bioxriv) were searched. Retrospective and prospective studies reporting clinical outcomes in cancer patients with laboratory confirmation or clinical diagnosis of COVID-19 and details of active or recent oncologic treatment were selected. Random-effects model was applied throughout meta-analyses. Summary outcome measure was the pooled odds ratio (OR) of death for active cancer therapy versus no active cancer therapy for each of the following modalities: recent surgery, chemotherapy, targeted therapy, immunotherapy, or chemoimmunotherapy.

**Results:** Sixteen retrospective and prospective studies (3558 patients) were included in the meta-analysis. Active chemotherapy was associated with higher risk of death compared to no active chemotherapy (OR, 1.60, 95% CI, 1.14–2.23). No significant association with risk of death was identified for active targeted therapy, immunotherapy, chemoimmunotherapy, or recent surgery. Meta-analysis of multivariate adjusted OR of death for active chemotherapy was consistently associated with higher risk of death compared to no active chemotherapy (OR, 1.42, 95% CI, 1.01–2.01).

**Conclusions:** Active chemotherapy appears to be associated with higher risk of death in cancer patients with COVID-19. Further research is necessary to characterize the complex interactions between active cancer treatment and COVID-19.

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COVID-19; immune therapy; chemotherapy; targeted therapy; chemoimmunotherapy

## Introduction

Cancer patients with coronavirus disease 2019 (COVID-19) suffer from worse outcomes compared to their non-cancer patient counterparts [1]. Furthermore, much has been discussed on whether active oncologic treatment is an additional risk factor for worse outcomes and if and whether practice patterns need to be changed to mitigate risks [2–4]. To date, numerous retrospective and prospective studies across the globe have been published evaluating the clinical characteristics of COVID-19 in cancer patients including the impact of active oncologic treatment on clinical outcomes in the setting of hospital admission for COVID-19. However, results of studies have remained conflicting and inconclusive with no clarity on which oncologic therapeutic modalities affect COVID-19 severity. Moreover, although multiple reviews by different experts have been published on this topic, conclusions have been disparate likely because only part of the available evidence had been reviewed in drawing the conclusion [5–7]. Therefore, we have conducted a systematic review and meta-analysis of the association between active oncologic treatment and adverse outcomes in cancer patients with laboratory confirmed or clinically diagnosed COVID-19 to determine the risk of active cancer treatment.

## Methods

### *Search strategy and study selection*

This study is registered on PROSPERO (CRD: 42020196760). Published articles reporting COVID-19 clinical outcomes including death in cancer patients from inception to July 1, 2020 were identified by searching PubMed and Embase. In addition, major conference proceedings including ASCO, ESMO, and AACR as well as the preprint databases medRxiv

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Supplemental data for this article can be accessed here.

and bioRxiv were searched. A search update was conducted on 10th October 2020. An example search strategy used for PubMed is as follows: 'COVID-19' AND ('neoplasms'[MeSH Terms]) OR 'neoplasms' OR 'cancer' AND ('humans'[MeSH Terms] AND English[lang]). Prospective or retrospective analyses published in English, reporting individual patient data were included in the quantitative meta-analysis. Review articles, case reports, and case series reporting less than three patients were excluded. Efforts to identify duplicate data among the selected studies included identifying whether specific studies were conducted in overlapping hospitals and contacting the corresponding authors of respective studies to specifically inquire whether duplicate data were reported. Furthermore, if any of the studies selected after assessment of eligibility were missing individual patient data necessary for quantitative meta-analysis, the respective corresponding authors were contacted to request the missing data. Database search and study selection were conducted by RP and SL then any discrepancies were resolved by the third reviewer, SK.

### Study quality and primary end points

Study quality was assessed using the Newcastle Ottawa Scale (NOS) for case control studies and cohort studies. The primary outcomes of interest were pooled odds ratio (OR) of all-cause death in cancer patients with laboratory confirmed or clinically diagnosed COVID-19 receiving active oncologic treatment versus not receiving active oncologic treatment. Treatment modalities were classified as surgery, chemotherapy, immunotherapy, targeted therapy, and chemoimmunotherapy. 'Recent' or 'active' treatment was not pre-defined for the meta-analysis and studies were included regardless of date of last treatment.

### Data extraction and statistical analysis

Author, date of publication, country, type of study, median and range of age, type of cancer included in the study, timing of most recent oncologic treatment, individual patient data for death stratified by treatment modality were extracted. In addition, if a study reported a multivariate analysis that evaluated risk of death associated with active cancer treatment adjusted by study-specified variables, the multivariate OR and 95% confidence interval (95% CI) were extracted to be used for pre-planned sensitivity analysis. The pre-specified minimum number of studies for data synthesis was three publications. Pooled ORs and 95% CI were calculated using a meta-analytical method that weighed the logarithm of the OR by the function of its variance for each study. OR of individual studies were combined using the random-effects meta-analysis fit with the Dersimonian-Laird Model. A pre-planned subgroup analysis was performed for definition of recency of treatment: studies defining active treatment as treatment received within approximately 4 weeks of COVID-19 diagnosis versus treatment received beyond 4 weeks of COVID-19 diagnosis (or undefined treatment timing). Publication bias was assessed using the Begg's funnel plot. Meta-analysis was performed using the package 'meta' of the R-project.

## Results

### Study characteristics and definitions

Following initial database search and screening, twenty-eight full-text articles were assessed for eligibility. Among these studies, twelve studies were excluded because individual patient data required for calculation of case fatalities in our study-specified treatment modality groups were not reported [8–18]. Among these studies, because of overlapping data of four patients with Garassino *et al*, Stroppa *et al*. was excluded from the analysis [19]. Finally, quantitative meta-analysis included sixteen studies ($n = 3558$ patients) in retrospective ($n = 15$) and prospective ($n = 1$) settings (Supplemental Figure 1). Studies were multi-national ($n = 2$), conducted in China ($n = 5$), USA ($n = 2$), United Kingdom ($n = 2$), Spain ($n = 2$), Brazil ($n = 1$), France ($n = 1$) or Italy ($n = 1$). Median ages were similar across studies (55–69). Two studies were conducted in lung cancer patients, one study in melanoma patients, one study in gynecologic cancer patients, and the rest of the studies in cancer patients regardless of tumor type. Study definitions of case fatality were variable: four studies reported all-cause death during hospital admission, two studies reported all-cause death during hospital admission or at home within the study-specified follow-up period, one study reported all-cause death within thirty days of COVID-19 diagnosis, one study reported death attributable to COVID-19 with no further specification of date cutoff, and eight studies did not report a date-specific definition for case fatality. Furthermore, for study definitions for timing of active cancer treatment, seven studies defined active treatment as treatment received within approximately one month of COVID-19 diagnosis (3 weeks–40 days), six studies as treatment received within approximately two to three months of COVID-19 diagnosis, and three studies did not specify a cutoff for last treatment received. Of note, two studies (Luo *et al*., Angelis *et al*.) reported different treatment timing definitions for different therapeutic modalities; for these two studies, treatment timing was considered to be defined as approximately one month of COVID-19 diagnosis based on the respective study's treatment timing of last cytotoxic chemotherapy. Criteria for COVID-19 diagnosis was laboratory confirmation of COVID-19 in ten studies, laboratory confirmation or clinical suspicion of COVID-19 in three studies, clinical diagnosis based on pre-specified criteria in three studies (Table 1).

### Pooled odds ratio of death

Overall, random-effects meta-analysis of pooled OR showed recent anti-cancer treatment was not associated with increased risk of death (OR, 1.16, 95% CI, 0.94–1.45) with moderate heterogeneity ($I^2$, 42%). Furthermore, pooled OR of death showed active chemotherapy was associated with higher risk of death compared to no active chemotherapy

**Table 1.** Characteristics of included studies.

| Author | Country | Median age (range) | *N* | Type of cancer | Study characteristics |
|---|---|---|---|---|---|
| Kuderer [23] | Multi-national | 66 (57–76) | 928 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: All-cause mortality within 30 days of COVID-19 diagnosis<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy and surgery<br>(2) Multivariate OR for CASE FATALITY: chemotherapy (adjusted by age, smoking, obesity)<br>-Treatment timing: last treatment received within the past 4 weeks<br>-COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 or presumptive diagnosis of COVID-19 infection |
| Yang [24] | China | 63 (56–70) | 205 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: during admission to hospital<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy and targeted therapy<br>(2) Multivariate OR for CASE FATALITY: chemotherapy (adjusted by sex, cancer type, time since diagnosis)<br>-Treatment timing: received within 4 weeks before symptom onset<br>-COVID-19 diagnosis: laboratory confirmed COVID-19 infection |
| Garassino [25] | Multi-national | 68 (61–75) | 200 | Lung cancer | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: during hospitalization or at home within follow up period<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, immunotherapy, targeted therapy, and chemoimmunotherapy<br>-Treatment timing: received within 3 months of COVID-19 diagnosis<br>-COVID-19 diagnosis: laboratory confirmed COVID-19 infection or suspected COVID-19 infection. |
| Wang [26] | China | 63 (55–70) | 283 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: due to any cause during follow up<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy<br>-Treatment timing: received within 3 months of hospitalization<br>-COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 infection |
| Lee [27] | UK | 69 (59–76) | 800 | Cancer type not pre-specified | -Prospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, immunotherapy, and targeted therapy<br>(2) Multivariate OR for CASE FATALITY: chemotherapy (adjusted by age, sex, comorbidities)<br>-Treatment timing: received within 4 weeks of COVID-19 diagnosis<br>-COVID-19 diagnosis: laboratory confirmed COVID-19 infection |
| Dai [28] | China | 64 (NR) | 105 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, immunotherapy, and targeted therapy<br>-Treatment timing: received within 40 days before onset of COVID-19 symptoms<br>-COVID-19 diagnosis: COVID-19 infection diagnosed by WHO interim guidance |
| Yu [29] | China | 66 (48–78) | 12 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, immunotherapy, targeted therapy, and chemoimmunotherapy<br>-Treatment timing: not further specified<br>-COVID-19 diagnosis: COVID-19 infection diagnosed by COVID-19 Diagnostic Criteria, 5$^{th}$ Edition |
| Luo [30] | USA | 68 (31–91) | 102 | Lung cancer | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: at home or inpatient<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, immunotherapy, and chemoimmunotherapy<br>-Treatment timing: received within 6 weeks (immunotherapy) or 3 weeks (chemotherapy or chemoimmunotherapy) of positive SARS-COV2 RT PCR<br>-COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 infection |

(*continued*)

**Table 1.** Continued.

| Author | Country | Median age (range) | *N* | Type of cancer | Study characteristics |
|---|---|---|---|---|---|
| Gonzalez-cao [31] | Spain | 69 (6–94) | 50 | Melanoma | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) CASE FATALITY: immunotherapy and targeted therapy<br>-Treatment timing: received within the last 8 weeks<br>-COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 infection |
| Zhang [32] | China | 66 (37–98) | 107 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: all-cause mortality<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, immunotherapy, targeted therapy, chemoimmunotherapy, and surgery.<br>-Treatment timing: received within the last 1 month<br>-COVID-19 diagnosis: COVID-19 infection diagnosed by COVID-19 Diagnostic Criteria, 5th Edition |
| Mehta [33] | USA | 69 (10–92) | 218 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy and immunotherapy<br>-Treatment timing: defined as patients on active treatment<br>-COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 infection |
| Bogani [34] | Italy | 65 (49–84) | 13 | Gynecologic cancer | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) CASE FATALITY: surgery, chemotherapy, immunotherapy, and targeted therapy.<br>-Treatment timing: unstated, but at least for chemotherapy and targeted therapy, patients are on active treatment -COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 infection |
| De Melo [35] | Brazil | 55 (1–88) | 181 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: death attributable to COVID-19<br>- Extracted data:<br>(1) CASE FATALITY: chemotherapy, targeted therapy, immunotherapy, surgery<br>-Treatment timing: within the last 60 days<br>-COVID-19 diagnosis: laboratory confirmed SARS-COV-2 infection |
| Angelis [36] | UK | 66 (IQR: 54–69) | 113 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: death not further specified<br>-Extracted data:<br>-Treatment timing: last chemotherapy received within 6 weeks or immunotherapy received within 3 months<br>-COVID-19 diagnosis: laboratory confirmed SARS-COV-2 infection |
| Yarza [37] | Spain | 66 (63–68) | 63 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: not further specified<br>-Extracted data:<br>(1) Multivariate OR for CFR: chemotherapy (adjusted by age, sex, ECOG, metastasis, previous VTE, COPD)<br>-Treatment timing: received within 4 weeks of hospitalization<br>-COVID-19 diagnosis: laboratory confirmed SARS-CoV-2 infection or COVID-19 infection based on clinical and radiological findings |
| Albiges [38] | France | 61 (52–71) | 178 | Cancer type not pre-specified | -Retrospective analysis<br>-Study Definitions:<br>(1) CASE FATALITY: presumably death during admission<br>-Extracted data:<br>(1) CASE FATALITY: chemotherapy, targeted therapy, immunotherapy<br>-Treatment timing: within the last 3 months<br>-COVID-19 diagnosis: majority laboratory confirmed diagnosis (93.8%) (remainder diagnosed based on radiologic criteria) |

(OR, 1.60, 95% CI, 1.14–2.23). Heterogeneity was moderate in the analysis for active chemotherapy versus no chemotherapy ($I^2 = 57\%$). On the other hand, recent surgery (OR, 1.14, 95% CI, 0.54–2.40), targeted therapy (OR, 0.74, 95% CI, 0.43–1.27), immunotherapy (OR, 0.89, 95% CI, 0.60–1.33), and chemoimmunotherapy (OR, 1.15, 95% CI, 0.62–2.12) were not associated with increased risk of death (Figure 1).

## Additional analyses

Random-effects meta-analysis of multivariate ORs of death showed active chemotherapy was associated with increased risk of death (OR, 1.42, 95% CI, 1.01–2.01). Of note, adjusted co-variates used in the calculation of the multivariate ORs were variable across the studies with age

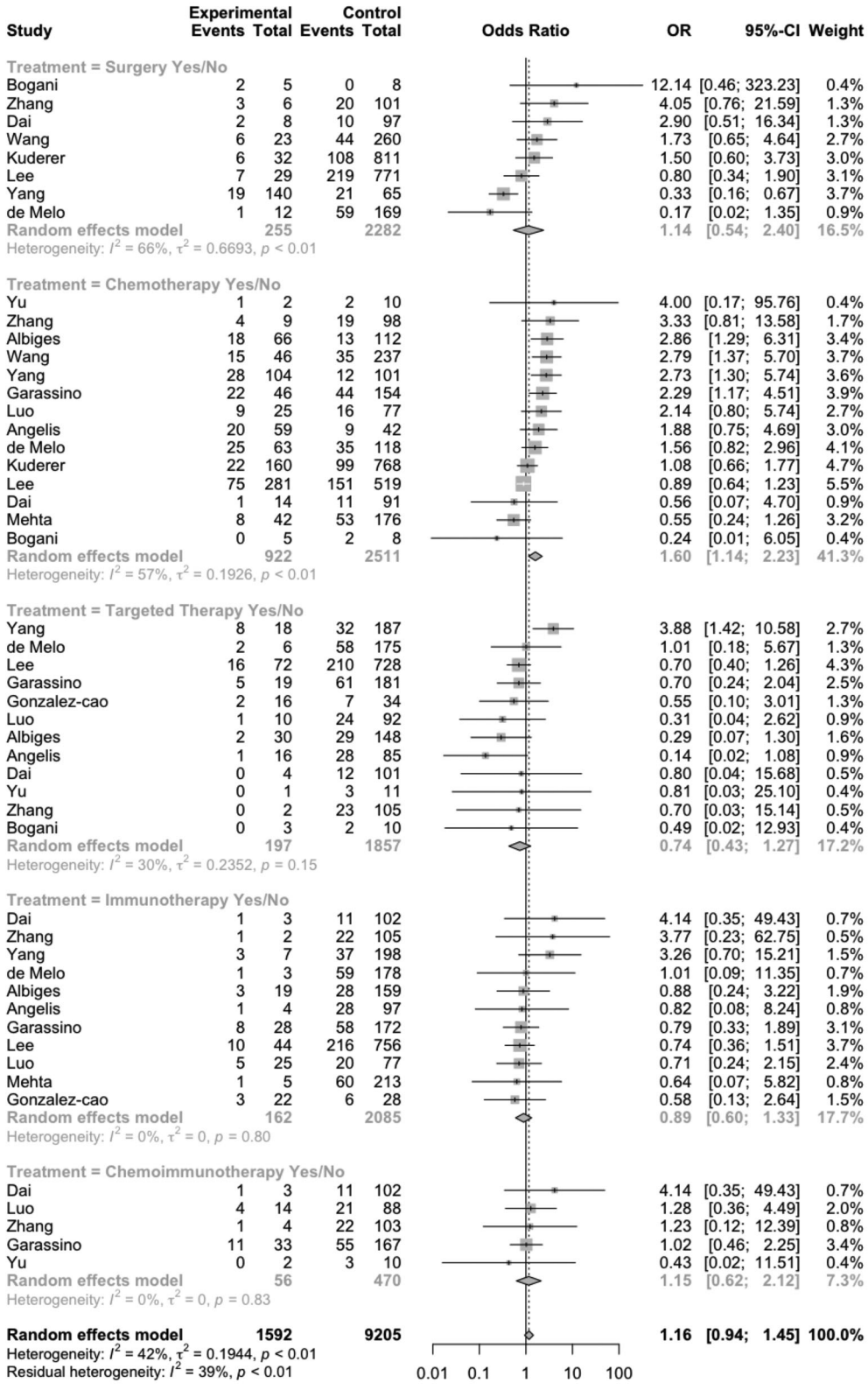


**Figure 1.** Meta-analysis of odds ratios for death comparing exposure versus no exposure to treatment of interest. Higher odds ratio indicates higher risk of death in the exposure to treatment group.

and sex the most common co-variates (3/4 studies) (Supplemental Figure 2). Meta-analyses of multivariate OR of death for surgery, immunotherapy, targeted therapy, and chemoimmunotherapy were not conducted due to limited number of studies. Subgroup analysis for OR of death for chemotherapy by timing of last treatment received showed no subgroup differences (within 4 weeks versus within a date greater than 4 weeks or date unstated, test for subgroup differences, $p$-value = .871) (Supplemental Figure 3).

An additional subgroup analysis was conducted for OR of all-cause death after exclusion of studies that defined COVID-19 based on non-laboratory-based criteria such as clinical or radiologic criteria. Results consistently showed increased risk of all-cause death with cytotoxic chemotherapy (OR, 1.57, 95% CI, 1.10–2.24), but not with other therapeutic modalities (Supplemental Figure 4)

### *Assessment of study bias and data overlap across studies*

Begg's test was not significant, demonstrating no obvious small-study publication bias (Supplemental Figure 5). NOS scale demonstrated good study quality (7–9) in all selected studies (Supplemental Table 1).

## Discussion

In summary, meta-analysis of published retrospective and prospective analyses show that in cancer patients with laboratory confirmed or clinically diagnosed COVID-19, active chemotherapy is associated with higher risk of death compared to no active chemotherapy. Recent surgery or active immunotherapy, targeted therapy, or chemoimmunotherapy were not associated with adverse COVID-19 outcomes.

Much has been debated on whether active cytotoxic chemotherapy increases risk of adverse outcomes in COVID-19. In this regard, our data provide evidence supporting for cytotoxic chemotherapy imparting higher risk of adverse outcomes. This is consistent with the long-established knowledge that patients on active chemotherapy are susceptible to respiratory infections including those of viral etiology, with the highest risk of pneumonia being in those who are older than 65 years and have severe neutropenia or lymphocytopenia [20]. Certain caveats should be considered, however, when interpreting these results. Namely, confounding by indication may contribute to the finding that active chemotherapy is associated with greater adverse outcomes. Indeed, patients on active cytotoxic chemotherapy are reasonably expected to have more advanced malignant disease and higher risk of all-cause death compared to who are not on active chemotherapy. However, based on our results meta-analysis of multi-variate adjusted ORs consistently show increased risk of death in patients on active chemotherapy, arguing against confounding by indication.

An increase in 30-day mortality and post-operative pulmonary complications compared to historical rates with peri-operative COVID-19 have been shown in a previously published international cohort study which is at odds with our study results that suggest no increase in risk of adverse outcomes [21]. Since the cohort study did not have a matched within-study control population who underwent similar surgeries and did not suffer peri-operative COVID-19, the conclusion derived from the study is limited, as the comparison is made to historical rates of peri-operative mortality and complications. There is the possibility that in the setting of COVID-19 pandemic, the proportion of lower-risk elective surgeries are lower which could skew the data. On the other hand, the limitation of our study is that a subgroup analysis could not be conducted due to limited number of studies to dissect whether the surgeries analyzed in the studies were major or minor or whether analyses were controlled for co-morbidities. Therefore, a high-quality study with a within-study control population is needed to derive a confidence conclusion in whether recent surgery is associated with increased risk of adverse outcomes in COVID-19.

Of note, variabilities existed across studies for their definitions of 'active' treatment, method of COVID-19 diagnosis, and case fatality. Consequently, the meta-analysis of all therapeutic modalities as well as the meta-analysis specifically of active chemotherapy versus no active chemotherapy demonstrated moderate heterogeneity (39%, 55% respectively). These results supported the use of the random-effects model for meta-analysis, which takes into account between-studies heterogeneity for calculation of summary estimate and consequently gives a wider confidence interval [22]. The meta-analysis of active chemotherapy versus no active chemotherapy demonstrated significantly increased risk despite this wide confidence interval.

This study has a number of limitations. First, the meta-analysis was based largely on retrospective studies which have their inherent biases. Second, beyond the increase in risk demonstrated for active chemotherapy, this study does not provide further insight on potential mechanisms of why risk of adverse COVID-19 outcomes will be increased. Ideally, large scale prospective studies are needed to further delineate the complex interactions among a patient's overall clinical condition, cancer characteristics such as affected organ, staging, treatment stage, as well as treatment details such as timing and dosing. Third, a number of high-quality studies with robust data were excluded from the meta-analysis due to non-reporting of individual patient data, which may have affected the summary outcome measure. However, publication bias analysis by Begg's funnel plot suggested no systematic publication bias was present. Lastly, this meta-analysis included studies where the diagnosis of COVID-19 was made based on clinical criteria, which introduces a degree of uncertainty. Nonetheless, these studies are the minority and subgroup analysis with studies exclusively with laboratory confirmed COVID-19 shows consistent data.

In conclusion, active cytotoxic chemotherapy appears to be associated with higher risk of adverse COVID-19 outcomes. Given the limitations of the study, we do not advocate or call for a change in practice patterns solely based on these results. However, further high-quality studies are warranted to better delineate the complex interactions underlying cytotoxic chemotherapy and COVID-19. Therefore, this study should be considered as hypothesis generating and further analysis is needed to confirm our findings.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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