



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to the Editor

Re: A systematic review and meta-analysis: The effect of active cancer treatment on severity of COVID-19 Clinical outcomes of SARS-CoV-2-infected cancer patients undergoing surgery



Caifeng Zou ^a, Yuting Huang ^b, Yuchi Ma ^c, Feng Yang ^{a,*}, Deliang Fu ^a

^a Department of Pancreatic Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China

^b Department of Medicine, University of Maryland Medical Center Midtown Campus, Baltimore, MD, USA

^c Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Received 28 March 2021; accepted 1 April 2021

Available online 15 May 2021

Recently we read with interest the systematic review and meta-analysis by Yekedüz *et al.* [1], in which they described the effects of anti-cancer treatments on the clinical outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients with cancer based on 16 observational studies [1]. They found that chemotherapy was associated with an increased risk of death from coronavirus disease 2019 (COVID-19) in patients with cancer but failed to show any significant association between other treatments, including surgery, and risks of severe events and death. As a result, they concluded that cancer surgery can be performed without higher risks of either severe events or death in patients with cancer along with COVID-19. We are pleased to see such work, as this is an important topic, with similar results published in other recent meta-analyses [2,3]. Because SARS-CoV-2 infections have been shown to

worsen outcomes in patients with cancer compared with non-cancer patients, additional data are needed to examine the effect of cancer treatments on infection. Nowadays, meta-analysis is generally accepted as a powerful tool to guide our evidence-based decision-making in clinical practice. The conclusion made by Yekedüz *et al.* [1] may encourage surgeons to operate without due caution. Therefore, we wish to express several concerns about the results on the relationship between cancer surgery and outcomes in patients with COVID-19.

Recent studies have confirmed that surgery increases death in patients with COVID-19 and is associated with malignant diseases and emergency or major surgeries [4]. Given this reason, guidelines propose to postpone elective surgery in patients with less aggressive cancers. This is consistent with a recent study showing that mortality is increased in surgical patients at a closer time interval between surgery and COVID-19 diagnosis [5]. The negative association between cancer surgery and risk of either severe events or death from COVID-19 shown by Yekedüz *et al.* [1] may be related to the small number of included studies. For instance, only three studies have been included for meta-analysis of severe COVID-19,

DOI of original article: <https://doi.org/10.1016/j.ejca.2020.09.028>.

* Corresponding author: Department of Pancreatic Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China.

E-mail address: yffudan98@126.com (F. Yang).

<https://doi.org/10.1016/j.ejca.2021.04.011>

0959-8049/© 2021 Elsevier Ltd. All rights reserved.

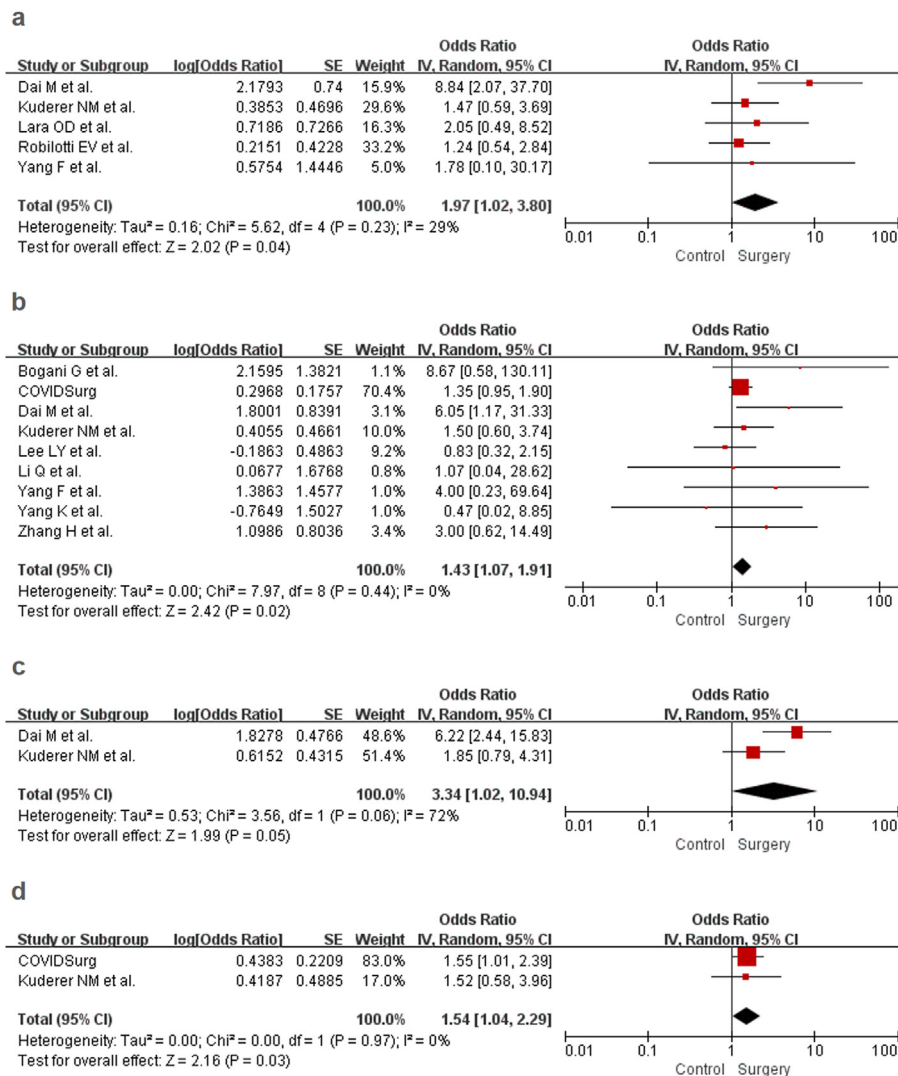


Fig. 1. Forestplots of risks of severe COVID-19 and death due to cancer surgery. (a) Unadjusted risk of severe COVID-19, (b) unadjusted risk of death, (c) adjusted risk of severe COVID-19, and (d) adjusted risk of death. * Adjusted variables for the study by Dai *et al.* included age, sex, diabetes, hypertension, smoking, and chronic obstructive pulmonary disease. * Adjusted variables for the study by Kuderer *et al.* included age, sex, smoking status, and obesity. * Adjusted Variables for the COVIDSurg study included age, sex, American Society of Anaesthesiologists grade, comorbidities, urgency/grade/timing of surgery. CI, confidence interval; IV, inverse variance; SE, standard error.

and four studies for meta-analysis of mortality. These are relatively low in comparison with studies included in similar meta-analyses [2,3]. The authors appear to have missed several studies published within the inclusion window from their search criteria unjustifiably [6–10]. Lack of inclusion of these prospective and retrospective series might influence their results. For example, they did not include the study by Lara *et al.* [6], which showed no association between recent major surgery and COVID-19 severity or mortality in 121 patients with gynaecologic cancer. This is also the case for other studies [7–10]. In addition, we would like to highlight a prospective cohort study conducted by the COVIDSurg Collaborative [4], showing significantly higher mortality in patients with peri-operative COVID-19 infection

undergoing surgery for malignant disease. Although the study is present in their references, it was not taken into account in the meta-analysis.

Given these issues, we would like to replicate the results of this meta-analysis on the association between cancer surgery and COVID-19 outcomes by including these missed studies [4,6–10]. Among a total of 11 cohort studies, two were prospective, and the remaining were retrospective. Five were performed in China, 2 in the United States, 1 in the United Kingdom, 1 in Italy, and two were conducted internationally. The number of cancer patients in the included studies ranged from 19 to 928, with 381 underwent surgical treatments. Nine studies were included assessing the risk of death from COVID-19

due to cancer surgery and five were included assessing the risk of severe COVID-19. We performed the statistical analyses by using the same methods as Yekeduz et al. [1] with the Review Manager software, version 5.3. In univariable analyses, cancer surgery was shown to increase the risk of severe COVID-19 (odds ratio [OR]: 1.97, 95% confidence interval [CI]: 1.02–3.80, $p = 0.04$). Heterogeneity between the included studies was not significant (Chi^2 : 5.62, I^2 : 29%, $p = 0.23$). Similarly, cancer surgery was also shown to increase the risk of death from COVID-19 (OR: 1.43, 95% CI: 1.07–1.91, $p = 0.02$). Heterogeneity was also not significant (Chi^2 : 7.97, I^2 : 0%, $p = 0.44$). Forest plots of unadjusted risks of severe COVID-19 and death due to cancer surgery are shown in Fig. 1a and b, respectively. In multivariable analyses, there was a borderline significant association between cancer surgery and severe COVID-19 risk (OR: 3.34, 95% CI: 1.02–10.94, $p = 0.05$), although heterogeneity was significant (Chi^2 : 3.56, I^2 : 72%, $p = 0.06$). A significant association between cancer surgery and risk of death from COVID-19 was shown after adjusting for confounding variables (OR: 1.54, 95% CI: 1.04–2.29). Heterogeneity was not significant (Chi^2 : 0.00, I^2 : 0%, $p = 0.97$). Forest plots of adjusted risks of severe COVID-19 and death due to cancer surgery were shown in Fig. 1c and d, respectively.

Overall, owing to the changes we made in the present meta-analysis, the results regarding cancer surgery by Yekedüz *et al.* [1] should be interpreted with caution. The small number of studies included in their meta-analysis reduces the generalisability of the provided conclusion. With data from 11 cohorts, we found that cancer surgery was positively associated with COVID-19 severe illness and death. Nevertheless, similar as the study by the authors, several limitations prevent us from reaching conclusive evidence. In most of the included studies, the number of patients with COVID-19 undergoing surgical treatment is relatively small, leading to heterogeneity between the studies. In addition, the included studies do not have uniform control groups (for instance, surgery versus no surgery, surgery versus other anti-cancer treatments, or surgery for cancer versus non-cancer patients), making the overall findings possibly distorted. Therefore, well-designed prospective studies with sufficient numbers of patients and appropriate controls are urgently needed, especially when the course of the pandemic is still uncertain.

In conclusion, our meta-analysis demonstrated the possible increase in risks of severe COVID-19 and death in SARS-CoV-2-infected cancer patients receiving surgical treatment. However, further analyses with more high quality studies are warranted to validate our results.

Funding

Supported by the National Key R&D Program of China No. 2017YFC1308604 (Dr Yang).

Conflict of interest statement

The authors declare no conflict of interest.

References

- [1] Yekedüz E, Utkan G, Ürün Y. A systematic review and meta-analysis: the effect of active cancer treatment on severity of COVID-19. *Eur J Canc* 2020;141:92–104.
- [2] Park R, Lee SA, Kim SY, de Melo AC, Kasi A. Association of active oncologic treatment and risk of death in cancer patients with COVID-19: a systematic review and meta-analysis of patient data. *Acta Oncol* 2021;60(1):13–9.
- [3] Liu H, Yang D, Chen X, Sun Z, Zou Y, Chen C, et al. The effect of anticancer treatment on cancer patients with COVID-19: a systematic review and meta-analysis. *Cancer Med* 2021;10(3): 1043–56.
- [4] COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet* 2020; 396(10243):27–38.
- [5] GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. *Anaesthesia* 2021;76(6):748–58.
- [6] Lara OD, O’Cearbhaill RE, Smith MJ, Sutter ME, Knisely A, McEachron J, et al. COVID-19 outcomes of patients with gynecologic cancer in New York City. *Cancer* 2020;126(19): 4294–303.
- [7] Bogani G, Ditto A, Bosio S, Brusadelli C, Raspagliesi F. Cancer patients affected by COVID-19: experience from Milan, Lombardy. *Gynecol Oncol* 2020;158(2):262–5.
- [8] Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Clinical characteristics and outcomes of cancer patients with COVID-19. *J Med Virol* 2020;92(10):2067–73.
- [9] Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multi-centre, retrospective, cohort study. *Lancet Oncol* 2020;21(7): 904–13.
- [10] Zhang H, Wang L, Chen Y, Wu Q, Chen G, Shen X, et al. Outcomes of novel coronavirus disease 2019 (COVID-19) infection in 107 patients with cancer from Wuhan, China. *Cancer* 2020; 126(17):4023–31.