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Review

A systematic review and meta-analysis: the effect of active cancer treatment on severity of COVID-19

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Abstract *Background:* The COVID-19 pandemic hit all over the world, and cancer patients are more vulnerable for COVID-19. The mortality rate may increase up to 25% in solid malignancies. In parallel to increased mortality rates among cancer patients, safety concerns regarding cancer treatment has increased over time. However, there were contradictory results for the cancer treatment during pandemic. In this study, we assessed the effect of cancer treatment on the severity of COVID-19.

Methods: The MEDLINE database was searched on September 01, 2020. Primary end-points were severe disease and death in the cancer patients treated within the last 30 days before COVID-19 diagnosis. Quality of included studies was assessed by Newcastle–Ottawa scale. The generic inverse-variance method was used to calculate odds ratios (ORs) for each outcome.

Results: Sixteen studies were included for this meta-analysis. Chemotherapy within the last thirty days before COVID-19 diagnosis increased the risk of death in cancer patients after adjusting for confounding variables (OR: 1.85; 95% confidence interval: 1.26–2.71). However, severe COVID-19 risk did not increase. Furthermore, targeted therapies, immunotherapy, surgery and radiotherapy did not increase the severe disease and death risk in cancer patients with COVID-19.

Conclusion: Chemotherapy increased the risk of death from COVID-19 in cancer patients. However, there was no safety concern for immunotherapy, targeted therapies, surgery and radiotherapy.

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1. Introduction

After reporting the first case of severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) infection in Wuhan, China, coronavirus disease 2019 (COVID-19) became a pandemic in a short time and hit all over the world. As of September 13, 2020, 28,584,158 confirmed cases and 916,955 deaths from COVID-19 were observed across the world [1]. Cancer patients are more vulnerable to COVID-19. The case fatality rate was 25% for solid organ malignancies; however, it is 2.3% for the general population [2,3]. In this context, since the beginning of the pandemic, there have been some concerns regarding cancer patients' treatment. We observe that the decision-making processes of oncologists are affected globally during the COVID-19 pandemic [4]. However, the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology recommended continuing cancer treatment by evaluating and discussing the risk and benefit of cancer treatment with each individual [5,6]. Despite no clear evidence for the safety of using chemotherapy (CT), immunotherapy, targeted therapies, radiotherapy (RT), and performing surgery in the cancer patients during the COVID-19 pandemic, cancer patients are treated in the light of these recommendations.

Over time, the knowledge about cancer treatment in the pandemic increased. Cancer and COVID registries, such as United Kingdom Coronavirus Cancer Monitoring Project, COVID-19 and Cancer Consortium, and numerous studies were published in the last three months particularly [7,8]. However, results from these studies were conflicting.

In the present meta-analysis, we aimed to evaluate cancer treatment's effect on the severity of COVID-19.

2. Methods

This meta-analysis was conducted in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

2.1. Study cohort

The MEDLINE database was searched on September 01, 2020, using the following keywords and boolean operators: '((('COVID-19' OR 'SARS-CoV2' OR 'SARS-CoV-2') AND (cancer OR neoplasm OR malignancy))'.

Inclusion criteria to select the studies: (a) patients − cancer patients receiving active cancer treatment and diagnosed with COVID-19; (b) intervention − cancer treatment within the last 30 days before COVID-19 diagnosis (i.e. CT, immunotherapy, targeted therapies, RT and surgery); (c) comparator − patients who do not receive cancer treatment whose effect is evaluated; (d) outcome − severe disease and death; (e) study design − prospective and retrospective studies. Pre-clinical studies, reviews, case reports, articles not in English and articles without full text were excluded.

2.2. Data extraction

According to the inclusion and exclusion aforementioned criteria, full-text articles of studies were assessed independently by two reviewers (E.Y., Y.Ü.). Data including the following headlines were extracted from the database: author names, publishing journals, the year of publication, the total number of patients in each study, the number of male patients, patient subgroups in the comparison groups, median−mean age, cancer treatment intervals before COVID-19 diagnosis, the number of patients in each cancer treatment subtype, unadjusted and adjusted odds ratios (ORs) for the severe disease and death for each cancer treatment subtype, and adjusting variables for multivariable analyses results.

2.3. Assessment quality of included studies

The quality of included studies was assessed independently by two reviewers (E.Y. and Y.Ü.) using the Newcastle−Ottawa scale (NOS) for case-control and cohort studies.

The total score was calculated using the following subsets: 1) selection, 2) comparability and 3) outcome. All subsets in the NOS for the cohort studies have subheadings. Subheadings for study selection: a) representativeness of the exposed cohort, b) selection of the non-exposed cohort, c) ascertainment of exposure, d) demonstration that the outcome of interest was not present at the start of study; the subheading for comparability: a) comparability of cohorts on the basis of the design or analysis; subheadings for outcome: a) assessment of the outcome, b) was follow-up long enough for outcomes to occur?, c) adequacy of follow-up of cohorts.

Similarly, the NOS for case-control studies has three subsets, including selection, comparability and exposure. All subsets also have subheadings. Subheadings for study selection: a) Is the case definition adequate?, b) representativeness of the cases, c) selection of controls, d) definition of controls; the subheading for comparability: a) comparability of cases and controls on the basis of the design or analysis; subheadings for exposure: a) ascertainment of exposure, b) the same method of ascertainment for cases and controls, c) the non-response rate.

Studies can earn four stars from selection, two stars from comparability and three stars from the outcome. Thus, the maximum score for each study can be nine stars [10].
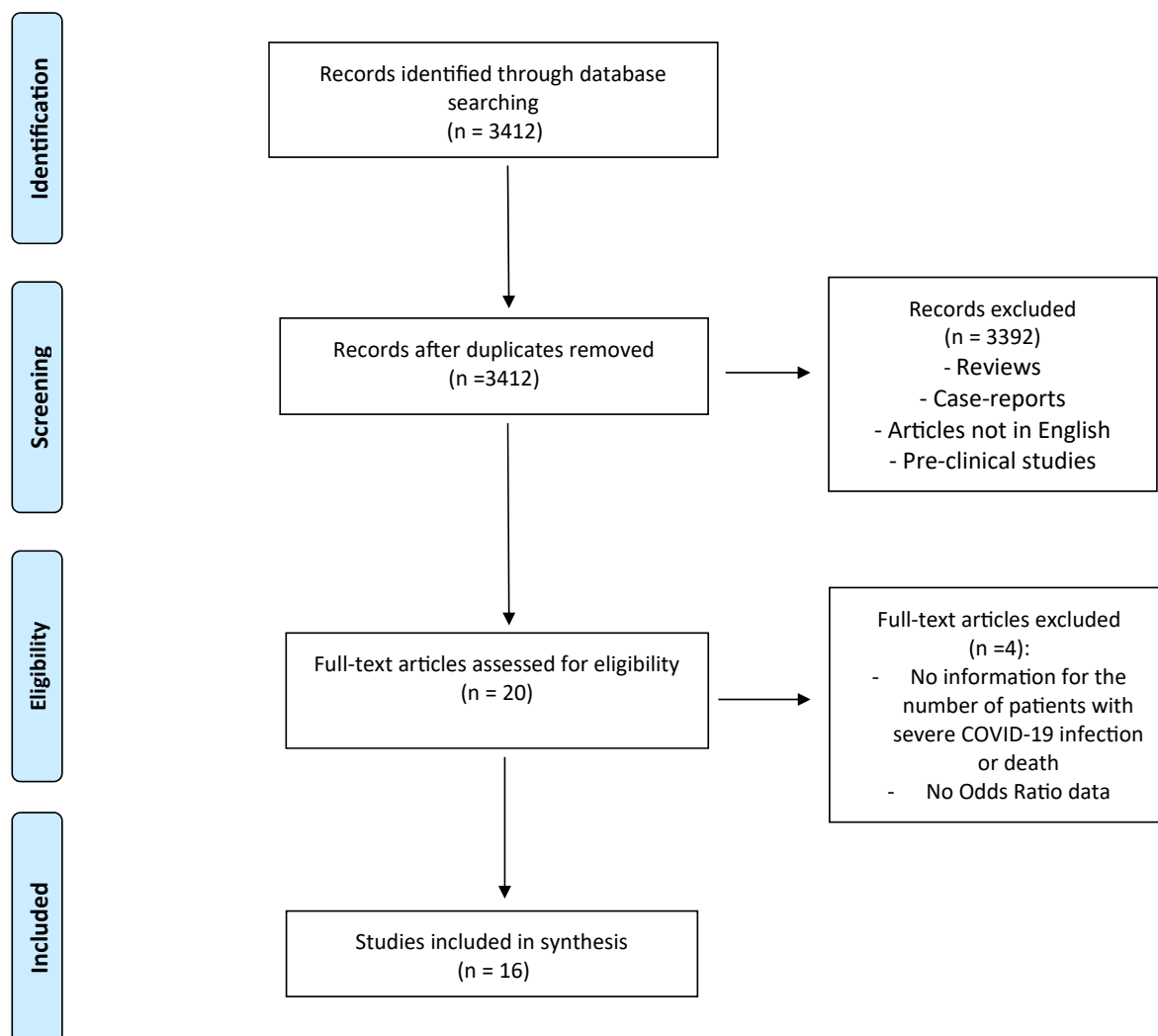
Fig. 1. The PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

2.4. Statistical analysis

The meta-analysis was performed using the generic inverse-variance method with a random-effects model to calculate each outcome's risk. The effect size was the OR and its 95% confidence interval (CI). The primary comparison was severe disease and death risk between SARS-CoV2 positive patients on active cancer treatment and those who were not on active cancer treatment. All analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The thresholds for statistical significance for overall effect tests were 0.05 and that for the tests of heterogeneity, within the overall, was 0.10. The I [2] coefficient was additionally used to quantify the degree of heterogeneity between the studies.

3. Results

After searching in accordance with the aforementioned criteria, we assessed twenty articles with full text.

Finally, we included sixteen studies for this meta-analysis. The PRISMA diagram for the selection process of the included studies is shown in Figure 1. We assessed the quality of the included studies by using the NOS. Results for the quality assessment of the included studies are shown in Table 1. Two of sixteen studies were prospective-cohort study [11,12]. Remaining studies were retrospective [7,13–25]. Four thousand five hundred ten cancer patients were included, and 53% of all patients (2421 patients) were male. Baseline characteristics of all the included studies are shown in Table 2.

3.1. Chemotherapy and severity of COVID-19

According to the analysis of univariable ORs, CT administration within the last 30 days before COVID-19 diagnosis did not increase the risk of severe disease and death in cancer patients (OR:1.02; 95% CI:0.67–1.53; p = 0.94 and OR:1.53; 95% CI:0.94–2.49; p = 0.09, respectively). There was heterogeneity between the included studies for severe disease and death (p = 0.05;

Table 1
The Newcastle−Ottawa scale for quality assessment of the studies.

Author, year	Selection	Comparability	Exposure/outcome	Total
Zhang L. *et al.*, Annals of Oncology [13]	★★	★	★★	★★★★★
Dai *et al.*, Cancer Discovery [14]	★	★★	★★★	★★★★★★
Stroppa *et al.*, Future Oncology [15]	★	★	★★	★★★★
Kuderer *et al.*, Lancet [7],[a]	★★★	★★	★★	★★★★★★★
Lee LY *et al.*, Lancet [12],[a]	★★★	★★	★★	★★★★★★★
Yang *et al.*, Lancet Oncology [16],[a]	★★★	★★	★★	★★★★★★★
Zhang H. *et al.*, Cancer [17]	★	★	★★	★★★★
Robilotti *et al.*, Nature Medicine [18]	★	★★	★★	★★★★★
Yarza *et al.*, European Journal of Cancer [19]	★★	★★	★★	★★★★★★
Li *et al.*, Leukemia [20]	★★	★★	★★	★★★★★★
Jee *et al.*, Journal of Clinical Oncology [21]	★★	★	★★	★★★★★
Sanchez-Pina *et al.*, European Journal of Haematology [22]	★★	★★	★★	★★★★★★
Lee LYW, Lancet Oncology [11],[a]	★★★	★★	★★	★★★★★★★
Pinato *et al.*, Cancer Discovery [23]	★★	★★	★★★	★★★★★★★
Assaad *et al.*, European Journal of Cancer [24]	★★	★★	★★	★★★★★★
Garassino *et al.*, Lancet Oncology [25]	★★	★★	★★	★★★★★★

[a] Quality assessed by using the Newcastle−Ottawa scale (NOS) for cohort studies. Remaining studies assessed by using the NOS for case control studies.

$I^2 = 57\%$ and $p < 0.001$; $I^2 = 77\%$, respectively). Forest plots of unadjusted ORs for the effect of CT on severe COVID-19 and risk of death from COVID-19 are shown in Figure 2a and b, respectively. Furthermore, in multivariable analysis, there was no significant difference between the CT and control groups in severe COVID-19 risk (OR:0.92; 95% CI:0.61−1.39). In contrast, risk of death from COVID-19 was higher in the CT group than that in the control group after adjusting for confounding variables (i.e. age, sex, cancer type, cancer treatment subtype, duration of cancer diagnosis, smoking status, obesity, performance status, presence of metastasis and comorbidities) (OR: 1.85; 95% CI:1.26−2.71). There was no heterogeneity between the included studies for adjusted results of severe disease and death ($p = 0.55$; $I^2 = 0\%$ and $p = 51$; $I^2 = 0\%$, respectively). Forest plots of adjusted ORs for the effect of CT on severe COVID-19 and death of risk from COVID-19 are shown in Figure 2c and d, respectively.

3.2. Immunotherapy and severity of COVID-19

In univariable analyses, immunotherapy within the last 30 days before COVID-19 diagnosis did not increase the risk of severe disease and death in cancer patients (OR:1.60; 95% CI:0.72−3.52; $p = 0.25$ and OR:1.12; 95% CI:0.60−2.08; $p = 0.72$, respectively). There was heterogeneity between the included studies for severe disease and death ($p = 0.03$; $I^2 = 64\%$ and $p = 0.05$; $I^2 = 52\%$, respectively). Forest plots of unadjusted ORs for the effect of immunotherapy on severe COVID-19 and risk of death from COVID-19 are shown in Figure 3a and b. Furthermore, there was no significant difference between the immunotherapy and control groups in the severe disease risk after adjusting for confounding variables (i.e. age, sex, race, performance score, smoking status, cancer type, corticosteroid use,

lymphopenia and presence of comorbidities and metastasis) (OR:1.02; 95% CI:0.10−10.40; $p = 0.98$). There was heterogeneity between the included studies for adjusted results of severe disease ($p = 0.03$; $I^2 = 79\%$). The forest plot of adjusted ORs for the effect of immunotherapy on severe COVID-19 is shown in Figure 3c.

3.3. Targeted therapies and severity of COVID-19

In univariable analyses, targeted therapies within the last 30 days before COVID-19 diagnosis did not increase the risk of severe disease and death in cancer patients (OR:0.39; 95% CI:0.18−0.86; $p = 0.02$ and OR:1.03; 95% CI:0.59−1.80; $p = 0.93$, respectively). There was heterogeneity between the included studies for death ($p = 0.08$; $I^2 = 46\%$). In contrast, there was no heterogeneity between the included trials for severe disease ($p = 0.30$; $I^2 = 16\%$). Forest plots of unadjusted ORs for the effect of targeted therapies on severe COVID-19 and risk of death from COVID-19 are shown in Figure 4a and b, respectively.

3.4. Cancer surgery and severity of COVID-19

In univariable analyses, cancer surgery within the last 30 days before COVID-19 diagnosis did not increase the risk of severe disease and death in cancer patients (OR:2.15; 95% CI:0.79−5.83; $p = 0.13$ and OR:1.51; 95% CI:0.69−3.30; $p = 0.30$, respectively). There was heterogeneity between the included studies for severe disease ($p = 0.06$; $I^2 = 64\%$). In contrast, there was no heterogeneity between the included trials for death ($p = 0.24$; $I^2 = 29\%$). Forest plots of unadjusted ORs for the effect of cancer surgery on severe COVID-19 and risk of death from COVID-19 are shown in Figure 5a and b, respectively.

Table 2
Characteristics of the included trials.

Author; journal	Type of the study	Number of patients	Number of male patients	Median age (IQR) (years)	Cancer treatment tnterval before COVID-19 infection (days)	Comparison group	Number of patients in chemotherapy group	Number of patients in immunotherapy group	Number of patients in targeted therapy group	Number of patients in surgery group	Number of patients in radiotherapy group	Number of patients in cancer treatment group
Zhang L. et al., Annals of Oncology [13]	Retrospective	28	17	65 (56–70)	30	Cancer patients with no treatment	N/A	N/A	N/A	N/A	N/A	12
Dai et al., Cancer Discovery [14]	Retrospective	105	57	64 (57–71)	40	Non-cancer patients	17	6	4	8	13	48
Stroppa et al., Future Oncology [15]	Retrospective	25	20	71[a]	N/A	Cancer patients with no treatment	8	4	N/A	N/A	N/A	12
Kuderer et al., Lancet [7]	Retrospective	928	468	66 (57–76)	28	Cancer patients with no treatment	160	38	75	32	12	366
Lee LY et al., Lancet [12]	Prospective cohort	800	449	69 (59–76)	28	Cancer patients with no treatment	281	44	72	29	76	528
Yang et al., Lancet Oncology [16]	Retrospective	205	96	63 (56–70)	28	Cancer patients with no treatment	31	4	12	4	9	54
Zhang H. et al., Cancer [17]	Retrospective	107	60	66 (36–98)	N/A	Cancer patients with no treatment	N/A	6	N/A	N/A	N/A	37
Robilotti et al., Nature Medicine [18]	Retrospective	423	212	N/A	30	Cancer patients with no treatment	191	31	N/A	N/A	N/A	N/A
Yarza et al., European Journal of Cancer [19]	Prospective cohort	63	34	N/A	28	Cancer patients treated other options	36	8	7	N/A	N/A	N/A
Li et al., Leukemia [20]	Retrospective	59	31	63 (54–70)	30	Cancer patients with no treatment	12	N/A	6	1	1	20
Jee et al., Journal of Clinical Oncology [21]	Retrospective	309	159	N/A	35	Cancer patients with no treatment	102	18	49	N/A	N/A	170
Sanchez-Pina et al., European Journal of Haematology [22]	Retrospective	39	23	64[a]	N/A	Cancer patients with no treatment	4	N/A	5	N/A	N/A	24
Lee LYW, Lancet Oncology [11]	Prospective cohort	227	148	69	28	Cancer patients with no treatment	108	N/A	N/A	N/A	N/A	N/A

Pinato et al., Cancer Discovery [23]	Retrospective	890	503	19 (mean)	68[a]	Cancer patients with no treatment	206	56	93	N/A	N/A	N/A
Assaad et al., European Journal of Cancer [24]	Retrospective	302	144	30	58[a]	Cancer patients with no treatment	137	26	N/A	N/A	N/A	137
Garassino et al., Lancet Oncology [25]	Retrospective	200	141	7 (median)	68 (61−75)	Cancer patients with no treatment	48	34	28	N/A	N/A	142

Abbreviations: COVID-19 = coronavirus disease 2019, IQR = interquartile range, N/A = data not available.

[a] Mean age.

3.5. RT and severity of COVID-19

In univariable analyses, RT within the last 30 days before COVID-19 diagnosis did not increase cancer patients' risk of death (OR:0.82; 95% CI:0.50−1.37; p = 0.46). There was no heterogeneity between the included trials (p = 0.40; I^2 = 0%). The forest plot of unadjusted ORs for the effect of RT on the risk of death from COVID-19 is shown in Figure 6.

3.6. Cancer treatment and severity of COVID-19

In univariable analyses, cancer treatment within the last 30 days before COVID-19 diagnosis did not increase the risk of severe disease and death in cancer patients (OR:0.89; 95% CI:0.53−1.49; p = 0.66 and OR:1.16; 95% CI:0.79−1.70; p = 0.44, respectively). There was heterogeneity between the included studies for severe disease and death (p < 0.001; I^2 = 85% and p = 0.007; I^2 = 62%, respectively). Forest plots of unadjusted ORs for the effect of cancer treatment on severe COVID-19 and risk of death from COVID-19 are shown in Figure 7a and b, respectively.

4. Discussion

To the best of our knowledge, this was the first comprehensive meta-analysis regarding the effect of cancer treatment on the clinical course of COVID-19.

In the present meta-analysis, we showed that active cancer treatment was not associated with an increased risk for severe disease and death from COVID-19. Furthermore, immunotherapy, targeted therapies, cancer surgery and RT did not increase the risk of severe disease and death from COVID-19 in cancer patients. According to multivariable analyses, although there was no increased risk for severe disease, the risk of death from COVID-19 was higher in the cancer patients administered CT.

During the COVID-19 pandemic, we learnt that age and male sex are associated with higher severe disease and mortality rates [26,27]. Furthermore, comorbidities and smoking affect the prognosis of COVID-19 [28,29]. In univariable analysis for the effect of CT on COVID-19 mortality, there was no increased risk of death from COVID-19 in cancer patientsadministered CT within the last 30 days before COVID-19 diagnosis. However, after adjusting for confounding variables, such as age, sex and comorbidities, we showed that CT increased the risk of death from COVID-19. In other words, CT was an independent risk factor for death in cancer patients with COVID-19.

At first look, it seems that there was a discrepancy in the results of the present meta-analysis. In the usual clinical course of a COVID-19, it is expected that severe pulmonary dysfunction and septic shock cause death

a

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dai et al.	1.2641	0.5394	10.9%	3.54 [1.23, 10.19]
Garassino et al.	−0.8699	0.5449	10.7%	0.42 [0.14, 1.22]
Kuderer et al.	−0.2877	0.2838	22.6%	0.75 [0.43, 1.31]
Pinato et al.	0.0953	0.2161	27.4%	1.10 [0.72, 1.68]
Robilotti et al.	0.0392	0.202	28.4%	1.04 [0.70, 1.55]
Total (95% CI)			**100.0%**	**1.02 [0.67, 1.53]**

Heterogeneity: Tau² = 0.11; Chi² = 9.29, df = 4 (P = 0.05); I² = 57%
Test for overall effect: Z = 0.08 (P = 0.94)

b

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Assaad et al.	−0.462	0.4358	11.0%	0.63 [0.27, 1.48]
Dai et al.	1.5129	0.6733	7.5%	4.54 [1.21, 16.99]
Garassino et al.	0.9322	0.4478	10.8%	2.54 [1.06, 6.11]
Kuderer et al.	0.0198	0.2576	14.1%	1.02 [0.62, 1.69]
Lee LY et al.	−0.2485	0.18	15.3%	0.78 [0.55, 1.11]
Li et al.	1.203	0.6914	7.3%	3.33 [0.86, 12.91]
Pinato et al.	−0.2485	0.1613	15.5%	0.78 [0.57, 1.07]
Sanchez−Pina et al.	2.5764	1.5754	2.2%	13.15 [0.60, 288.34]
Stroppa et al.	−0.3567	0.9178	5.1%	0.70 [0.12, 4.23]
Yang et al.	1.8733	0.4353	11.0%	6.51 [2.77, 15.28]
Total (95% CI)			**100.0%**	**1.53 [0.94, 2.49]**

Heterogeneity: Tau² = 0.38; Chi² = 39.14, df = 9 (P < 0.0001); I² = 77%
Test for overall effect: Z = 1.69 (P = 0.09)

c

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Jee et al.	−0.1278	0.2216	88.8%	0.88 [0.57, 1.36]
Yarza et al.	0.3075	0.6244	11.2%	1.36 [0.40, 4.62]
Total (95% CI)			**100.0%**	**0.92 [0.61, 1.39]**

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)

d

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Kuderer et al.	0.3853	0.2855	46.4%	1.47 [0.84, 2.57]
Lee LYW et al.	0.7372	0.3321	34.3%	2.09 [1.09, 4.01]
Yang et al.	1.2556	0.5649	11.8%	3.51 [1.16, 10.62]
Yarza et al.	0.47	0.7073	7.6%	1.60 [0.40, 6.40]
Total (95% CI)			**100.0%**	**1.85 [1.26, 2.71]**

Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 3 (P = 0.55); I² = 0%
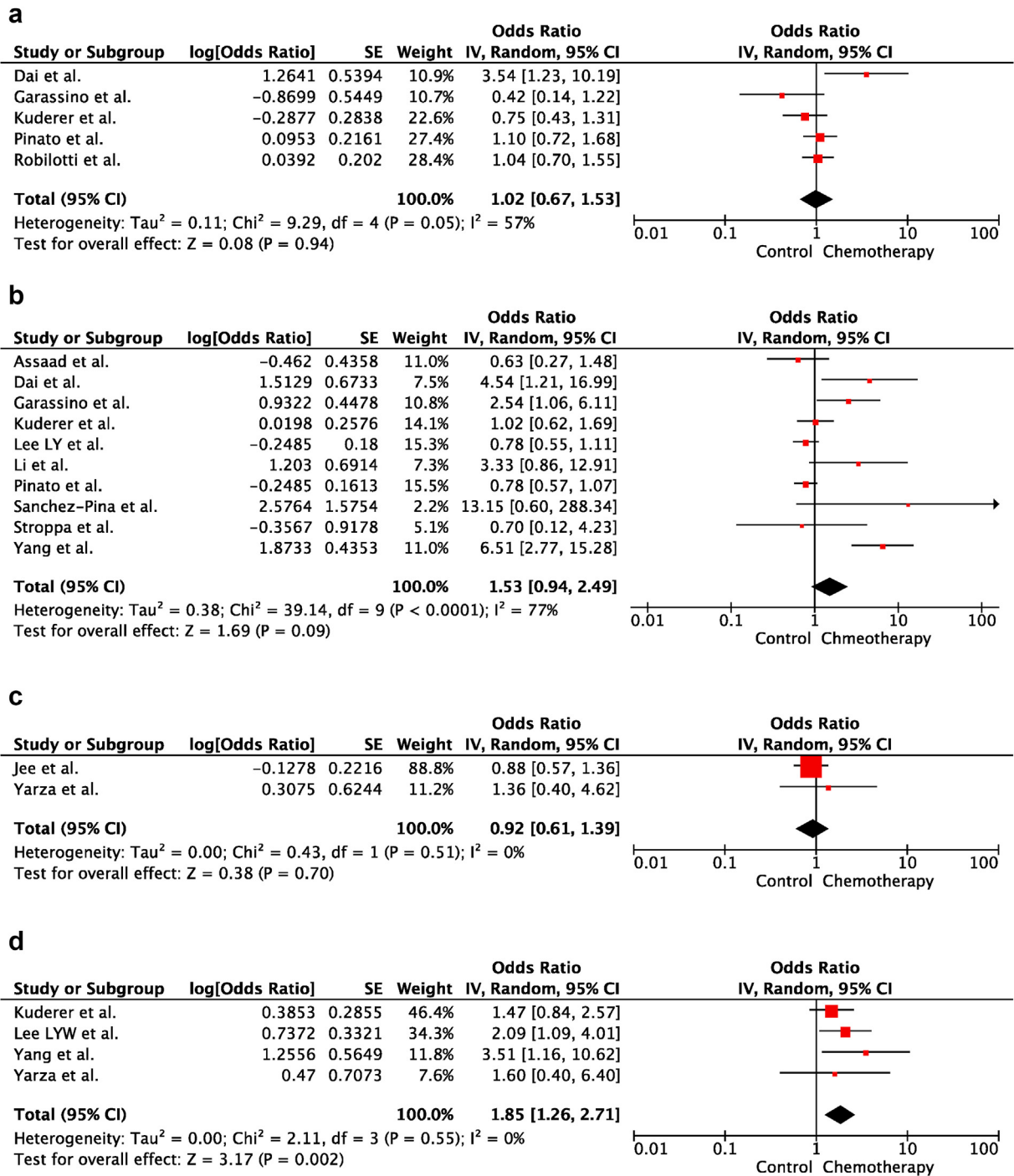Test for overall effect: Z = 3.17 (P = 0.002)

Fig. 2. (a) The forest plot of unadjusted severe COVID-19 risk due to chemotherapy. (b) The forest plot of unadjusted risk of death from COVID-19 due to Chemotherapy. (c) The forest plot of adjusted severe COVID-19 risk due to chemotherapy. ∗Adjusted variables for the study of Jee et al. [21]: age, BMI, sex, performance score, smoking, comorbidities, malignancy type, cancer remission status, neutropenia and lymphopenia. ∗Adjusted variables for the study of Yarza et al. [19]: age, sex, performance score, presence of metastasis, previous venous thromboembolic event, chronic obstructive pulmonary disease. (d) The forest plot of adjusted risk of death from COVID-19 due to chemotherapy. ∗ Adjusted variables for the study of Kuderer et al. [7]: age, sex, smoking status and obesity. ∗ Adjusted variables for the study of Lee et al. [8]: cancer treatment subtype. ∗ Adjusted variables for the study of Yang et al. [16]: sex, cancer type, duration of cancer diagnosis. ∗ Adjusted Variables for the study of Yarza et al. [19]: age, sex, performance score, presence of metastasis, previous venous thromboembolic event, chronic obstructive pulmonary disease. CI, confidence interval; IV, inverse variance; SE, standard error.

a

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dai et al.	2.3618	0.8749	13.1%	10.61 [1.91, 58.94]
Garassino et al.	−0.6812	0.5874	19.8%	0.51 [0.16, 1.60]
Pinato et al.	0.1133	0.327	27.8%	1.12 [0.59, 2.13]
Robilotti et al.	0.9282	0.3891	25.9%	2.53 [1.18, 5.42]
Zhang H et al.	0.1655	0.857	13.4%	1.18 [0.22, 6.33]
Total (95% CI)			**100.0%**	**1.60 [0.72, 3.52]**

Heterogeneity: Tau^2 = 0.48; Chi^2 = 11.10, df = 4 (P = 0.03); I^2 = 64%
Test for overall effect: Z = 1.16 (P = 0.25)

b

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Assaad et al.	−0.0513	0.6811	13.0%	0.95 [0.25, 3.61]
Dai et al.	2.205	0.8884	9.1%	9.07 [1.59, 51.74]
Garassino et al.	0.3257	0.4959	18.0%	1.38 [0.52, 3.66]
Lee LY et al.	−0.5108	0.3704	22.4%	0.60 [0.29, 1.24]
Pinato et al.	−0.2231	0.2855	25.6%	0.80 [0.46, 1.40]
Stroppa et al.	−2.1203	1.6178	3.4%	0.12 [0.01, 2.86]
Zhang H et al.	1.2179	0.938	8.4%	3.38 [0.54, 21.25]
Total (95% CI)			**100.0%**	**1.12 [0.60, 2.08]**

Heterogeneity: Tau^2 = 0.31; Chi^2 = 12.39, df = 6 (P = 0.05); I^2 = 52%
Test for overall effect: Z = 0.35 (P = 0.72)

c

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Robilotti et al.	1.0438	0.4228	57.3%	2.84 [1.24, 6.50]
Yarza et al.	−1.3471	1.0094	42.7%	0.26 [0.04, 1.88]
Total (95% CI)			**100.0%**	**1.02 [0.10, 10.40]**

Heterogeneity: Tau^2 = 2.26; Chi^2 = 4.77, df = 1 (P = 0.03); I^2 = 79%
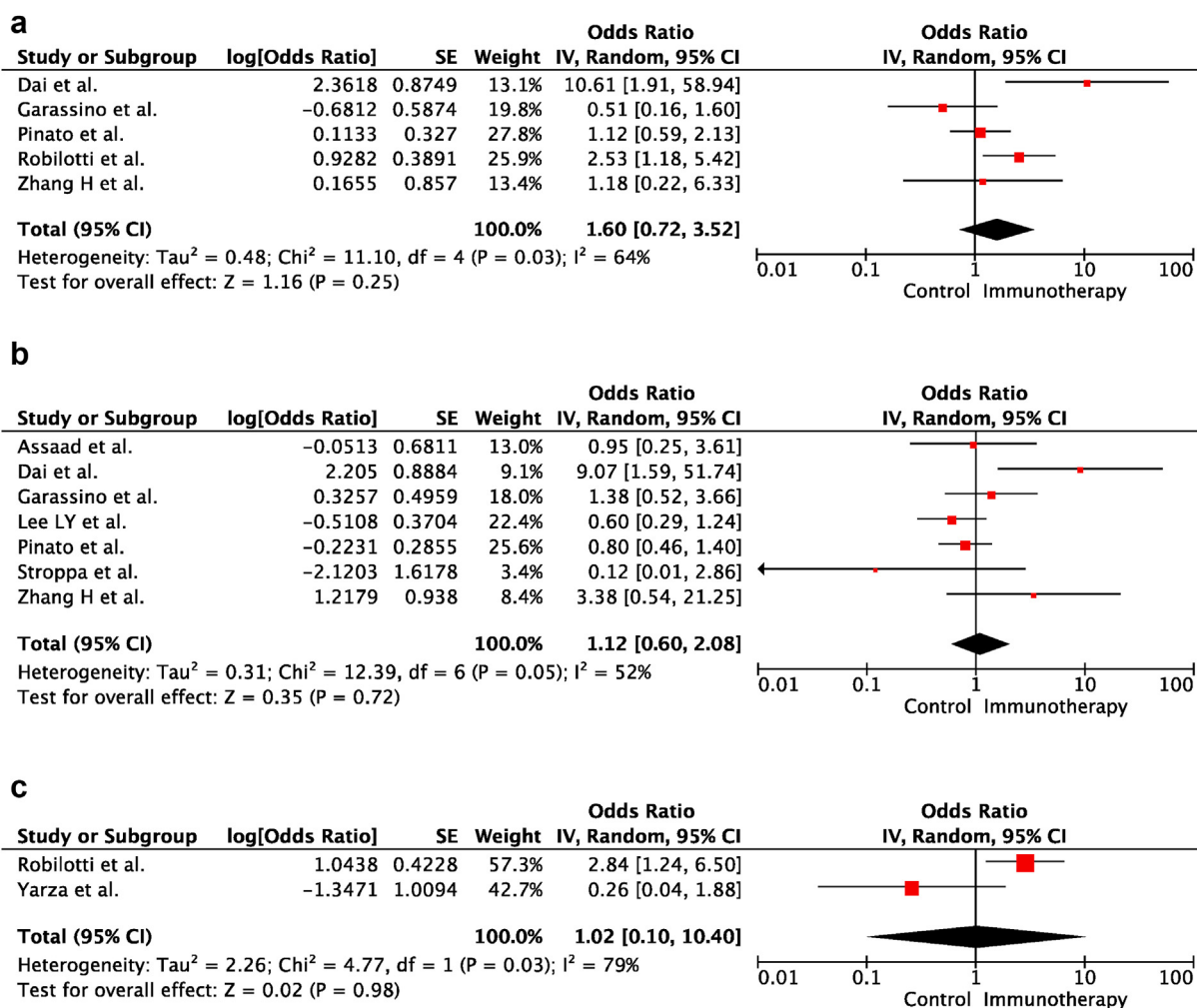Test for overall effect: Z = 0.02 (P = 0.98)

Fig. 3. (a) The forest plot of unadjusted severe COVID-19 Risk Due to Immunotherapy. (b) The forest plot of unadjusted risk of death from COVID-19 due to immunotherapy. (c) The forest plot of adjusted severe COVID-19 risk due to immunotherapy. *Adjusted variables for the study of Robilotti *et al.*: age, race, smoking, asthma, cancer type, comorbidities, corticosteroid use/lymphopenia. * Adjusted variables for the study of Yarza *et al.* [19]: age, sex, performance score, presence of metastasis, previous venous thromboembolic event, chronic obstructive pulmonary disease. CI, confidence interval; IV, inverse variance; SE, standard error.

from COVID-19. Indeed, dyspnoea is the most common symptom of COVID-19 [30]. Furthermore, acute respiratory distress syndrome (ARDS) and septic shock were the most common causes of death [31]. However, it is well known that cytokine storm and macrophage-activation syndrome (MAS) led by SARS-CoV-2 is the main reason for ARDS and septic shock in patients with COVID-19. Uncontrolled inflammatory response against viral infection causes severe organ damage and, thus, pulmonary and cardiac dysfunction [32,33]. To make this robust and surge inflammatory response, individuals should have an effective immune system. However, the negative impact of CT on the immune system is well known for years [34]. Furthermore, after the mitigation of immune functions by CT, recovery of the immune system might take a long time [35]. An impaired immune system might cause a decreased inflammatory response against SARS-CoV-2 and, thus,

protecting from cytokine storm and MAS [36]. Immune dysfunction led by CT might cause COVID-19 without apparent clinical manifestations. On the other hand, studies established that immunocompromised patients had similar clinical findings with immunocompetent patients [37]. Furthermore, although no apparent clinical findings of COVID-19, patients with immune dysfunction have an increased mortality [38]. It is worth noting that there is no convincing data to conclude a strict result regarding the immune system's effect on the severity of COVID-19. There was no clear reason to explain the increased mortality without severe disease in cancer patients administered CT. Besides the typical clinical course of severe COVID-19, the sudden death due to cardiac arrhythmia and injury was also reported [39]. However, there is no obvious evidence for the increased risk of sudden cardiac death in cancer patients with COVID-19. Furthermore, increased risk
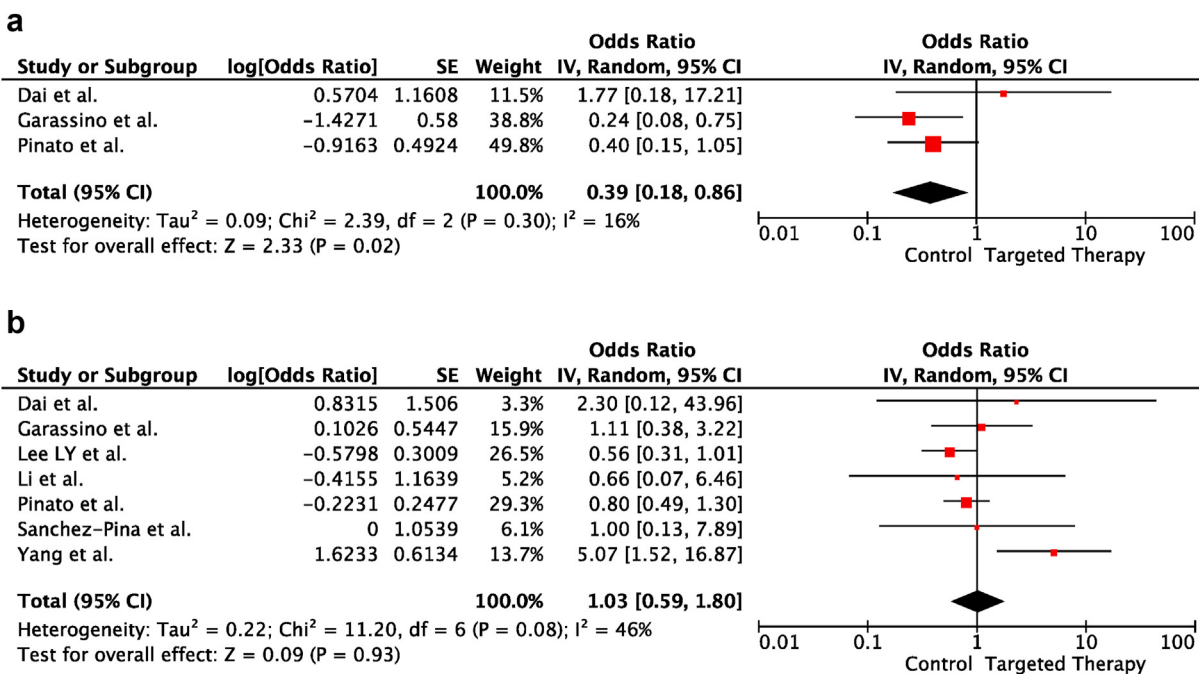
a

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dai et al.	0.5704	1.1608	11.5%	1.77 [0.18, 17.21]
Garassino et al.	−1.4271	0.58	38.8%	0.24 [0.08, 0.75]
Pinato et al.	−0.9163	0.4924	49.8%	0.40 [0.15, 1.05]
Total (95% CI)			**100.0%**	**0.39 [0.18, 0.86]**

Heterogeneity: Tau² = 0.09; Chi² = 2.39, df = 2 (P = 0.30); I² = 16%
Test for overall effect: Z = 2.33 (P = 0.02)

b

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dai et al.	0.8315	1.506	3.3%	2.30 [0.12, 43.96]
Garassino et al.	0.1026	0.5447	15.9%	1.11 [0.38, 3.22]
Lee LY et al.	−0.5798	0.3009	26.5%	0.56 [0.31, 1.01]
Li et al.	−0.4155	1.1639	5.2%	0.66 [0.07, 6.46]
Pinato et al.	−0.2231	0.2477	29.3%	0.80 [0.49, 1.30]
Sanchez−Pina et al.	0	1.0539	6.1%	1.00 [0.13, 7.89]
Yang et al.	1.6233	0.6134	13.7%	5.07 [1.52, 16.87]
Total (95% CI)			**100.0%**	**1.03 [0.59, 1.80]**

Heterogeneity: Tau² = 0.22; Chi² = 11.20, df = 6 (P = 0.08); I² = 46%
Test for overall effect: Z = 0.09 (P = 0.93)

Fig. 4. (a) The forest plot of unadjusted severe COVID-19 risk due to targeted therapy. (b) The forest plot of unadjusted risk of death from COVID-19 due to targeted therapy. CI, confidence interval; IV, inverse variance; SE, standard error.

of death in cancer patients administered CT within the last 30 days before COVID-19 diagnosis might be associated with the increased adverse event (AEs) rates of CT regardless of COVID-19. Neutropenic fever and sepsis are the most common causes of death from CT administered within the last 30 days [40]. However, there was no additional information regarding deaths from CT-related AEs in the included studies. In addition, there was no information for the primary administration purpose of CT. If most patients administered CT have advanced disease and are administered palliative CT, it is expected that mortality rates are higher than the control arm. In this regard, it could be explained why mortality rates were higher in the CT group without severe disease manifestations of COVID-19.

Targeted therapies have less risk for neutropenia or leukopenia than CT [41]. In this context, the

a

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dai et al.	2.1793	0.74	24.9%	8.84 [2.07, 37.70]
Kuderer et al.	0.3853	0.4696	36.4%	1.47 [0.59, 3.69]
Robilotti et al.	0.2151	0.4228	38.7%	1.24 [0.54, 2.84]
Total (95% CI)			**100.0%**	**2.15 [0.79, 5.83]**

Heterogeneity: Tau² = 0.49; Chi² = 5.59, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 1.51 (P = 0.13)

b

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dai et al.	1.8001	0.8391	17.8%	6.05 [1.17, 31.33]
Kuderer et al.	0.4055	0.4661	39.4%	1.50 [0.60, 3.74]
Lee LY et al.	−0.1863	0.4863	37.6%	0.83 [0.32, 2.15]
Li et al.	0.0677	1.6768	5.3%	1.07 [0.04, 28.62]
Total (95% CI)			**100.0%**	**1.51 [0.69, 3.30]**

Heterogeneity: Tau² = 0.19; Chi² = 4.25, df = 3 (P = 0.24); I² = 29%
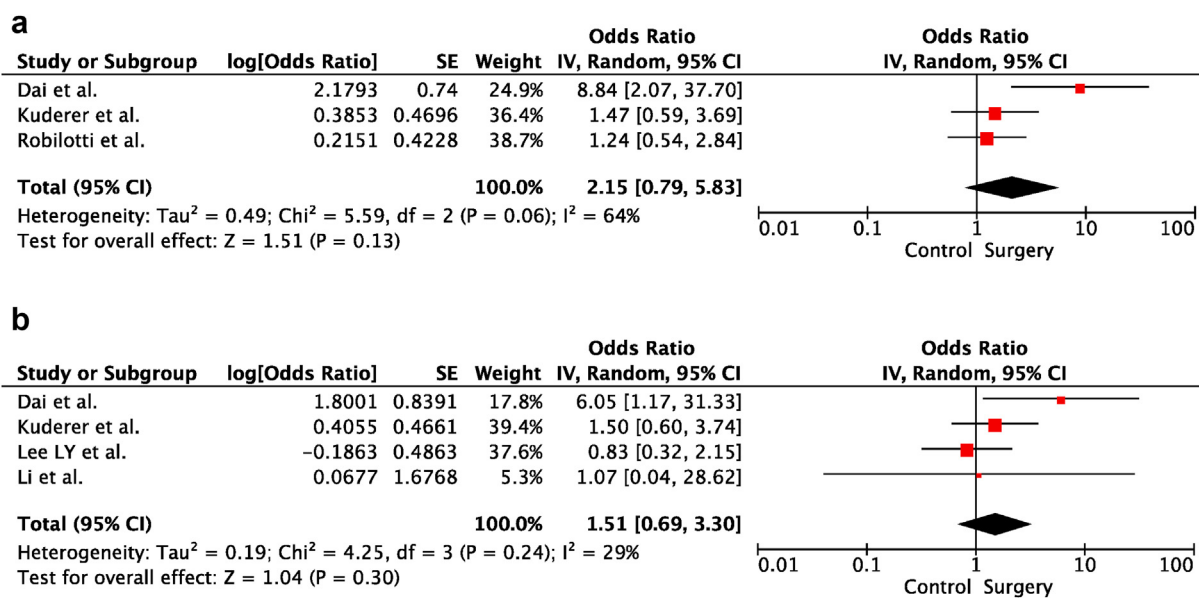Test for overall effect: Z = 1.04 (P = 0.30)

Fig. 5. (a) The forest plot of unadjusted severe COVID-19 risk due to surgery. (b) The forest plot of unadjusted risk of death from COVID-19 due to surgery. CI, confidence interval; IV, inverse variance; SE, standard error.
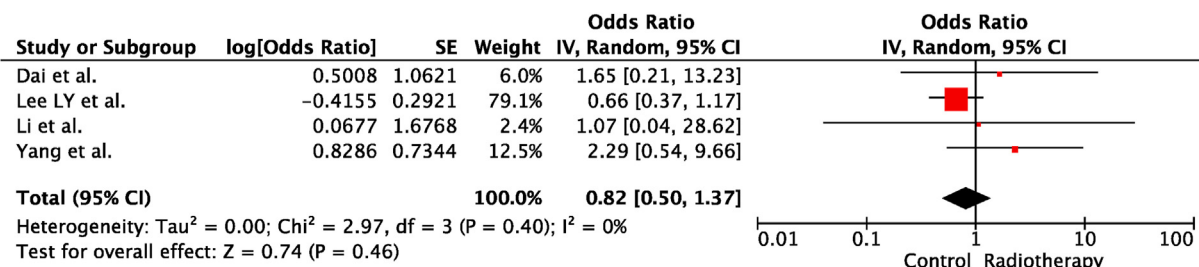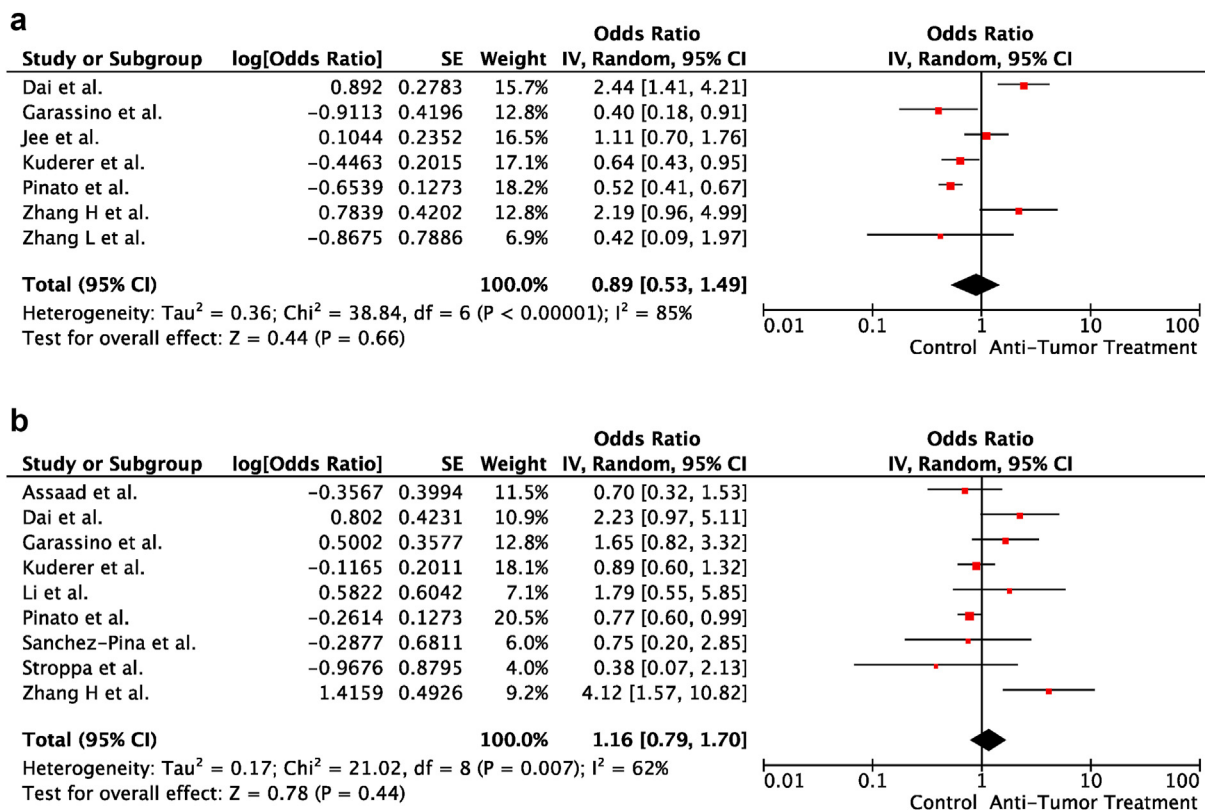
Fig. 6. The forest plot of unadjusted risk of death from COVID-19 due to radiotherapy. IV, inverse variance; SE, standard error

immunocompromising effect of targeted agents is lower than that of CT. On the other hand, targeted therapies have various effects on the immune functions. They may enhance T-cell immunity or suppress the immune system [42]. There has been no security concern regarding targeted agents in treating cancer patients during the pandemic. Furthermore, the ESMO did not recommend the interruption of targeted therapies [5]. Our results were consistent with the previous expectations. Furthermore, we showed that targeted therapy decreased the risk of severe COVID-19. Although this result needs more evidence, it may be associated with the enhancing effect of targeted therapeutic agents, such as imatinib, sunitinib, axitinib and trametinib, on the immune system [42]. Besides the immune-enhancing effects of targeted agents, Weisberg et al. [43] recommended the repurposing of these agents for treating COVID-19 due

to their antiviral, immunomodulatory and antifibrotic effects. Indeed, particularly Abelson (Abl) kinase inhibitors (i.e. imatinib, dasatinib, nilotinib) showed antiviral effect on severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infections [44].

Immunotherapeutic agents, such as programmed death-1, programmed death ligand-1 or cytotoxic T lymphocyte associated−antigen-4 inhibitors show their effect enhancing T-cell functions against cancer cell or virus [45−47]. In our previous case report, we observed that nivolumab within the last seven days before diagnosis provided a good clinical course of COVID-19 in a seventy-five-year-old female malign melanoma patient [61]. Furthermore, there are still ongoing clinical trials investigating the effect of nivolumab on COVID-19 (NCT04413838, NCT04343144 and NCT04356508).

Fig. 7. (a) The forest plot of unadjusted severe COVID-19 risk due to cancer treatment. (b) The forest plot of unadjusted risk of death from COVID-19 due to cancer treatment. CI, confidence interval; IV, inverse variance; SE, standard error.

One of the main concerns regarding the use of immune checkpoint inhibitors (ICIs) during pandemic is that the clinical findings of pneumonitis due to ICIs or pneumonia of COVID-19 may confuse the patient management. Clinical symptoms of COVID-19 pneumonia and ICI-related pneumonitis are very similar [49]. However, the present meta-analysis established that ICIs can be used in treating cancer patients during pandemic without concerns about the risk of severe disease and mortality.

Postoperative pulmonary complications are challenging for all patients. The spectrum of these complications changes from minimal atelectasis to severe respiratory failure. Pulmonary embolism, pleural effusion, infections, pneumothorax and aspiration pneumonitis are the other pulmonary complications of the postoperative setting [50]. Amid the COVID-19 pandemic, we have a new infectious agent, SARS-CoV-2. Nepogodiev et al. [51]showed that the postoperative complications and mortality risk were higher in the patients infected by SARS-Cov-2 in the perioperative setting. In compliance with the concerns in this study's results, most elective surgical procedures were postponed across the world. However, articles published recently did not show increased mortality and severe disease risk in patients who had undergone elective surgery [52,53]. Similarly, according to the results of the present meta-analysis, it seems that cancer surgery can be performed without increased risk for severe disease and death during the pandemic.

During pandemic, authors and guidelines recommended the assessment of each patient for the risk and benefit of RT. They also recommended that hypofractionated regimens should be encouraged. Furthermore, active surveillance may be a good option in the low-risk prostate cancer patients [54]. The mitigation of patient admissions to the hospitals is the main purpose of all these recommendations. On the other hand, postponing elective surgeries during the pandemic increased the administration of CT and RT as well [55]. RT-induced lymphopenia (RTIL) is the main concern for the use of RT during pandemic because of lymphopenia is the poor prognostic indicator for COVID-19 [56−58]. Despite the lymphopenia effect of RT, stereotactic procedures can be used safely without an increased risk for RTIL [59]. Indeed, during the pandemic, stereotactic body RT is a good alternative for surgery. Furthermore, the authors recommended that RT can be performed safely during the pandemic [60]. In parallel to this recommendation, we did not show a safety concern regarding RT administration within the last 30 days before the COVID-19 diagnosis.

We had some limitations in the present meta-analysis. First, fourteen of sixteen studies included retrospective data. Only two trials assessed patients prospectively. Second, we only evaluated multivariable results in the severe disease risk and death risk for CT and severe disease risk for immunotherapy. Because of confounding factors, such as age, sex and comorbidities are crucial on the prognosis of COVID-19, univariable analyses may not show the real effect of cancer treatment on the severity of COVID-19. Third, there was no information in the articles regarding cancer treatment, whether palliative or not. Indeed, the rates of advanced cancer patients may affect the severity and mortality of COVID-19. Fourth, there was also no information regarding death from treatment-related complications or COVID-19. At that point, if we know the rate of cancer treatment related-death in the studies, it may explain the effect of CT on the mortality risk despite without any increased risk for severe disease. Fifth, the numbers of included studies were different for each outcome, and this led to heterogeneity between the outcomes. Sixth, we only assessed the risk of death from COVID-19 in the patients administered RT. There was no information for the severe disease risk in the included studies. Seventh, comparison arms were different in the included studies. Fourteen studies included patients without cancer treatment in the comparison group. In contrast, one study included remaining cancer patients except for evaluated treatment type, and one study included no cancer patients in the comparison groups. Eight, we did no assessed the effect of hormonal therapy on the severity of COVID-19.

In conclusion, cancer treatment did not increase the severe disease and mortality risk in cancer patients treated within the last 30 days before COVID-19 diagnosis. However, being on active CT was associated with an increased mortality risk in cancer patients with the COVID-19. Though, for each patient, expected benefit and toxicity of treatment should be discussed widely with the patient, and, when necessary, a decision should be made in a multidisciplinary tumour board according to the treatment goal.

Author contribution

All authors contributed equally to this manuscript.

This manuscript is a meta-analysis and not required an ethical approval.

All authors confirm that there is a data set available when needed.

Conflict of interest statement

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