The impact of anti-tumor approaches on the outcomes of cancer patients with COVID-19: a meta-analysis based on 52 cohorts incorporating 9231 participants

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Abstract

Background: This study was designed to investigate the impact of anti-tumor approaches (including chemotherapy, targeted therapy, endocrine therapy, immunotherapy, surgery and radiotherapy) on the outcomes of cancer patients with COVID-19.

Methods: Electronic databases were searched to identify relevant trials. The primary endpoints were severe disease and death of cancer patients treated with anti-tumor therapy before COVID-19 diagnosis. In addition, stratified analyses were implemented towards various types of anti-tumor therapy and other prognostic factors. Furthermore, odds ratios (ORs) were hereby adopted to measure the outcomes with the corresponding 95% confidence intervals (CIs).

Results: As indicated in the study consisting of 9231 individuals from 52 cohorts in total, anti-tumor therapy before COVID-19 diagnosis could elevate the risk of death in cancer patients (OR: 1.21, 95% CI: 1.07–1.36, P = 0.0026) and the incidence of severe COVID-19 (OR: 1.19, 95% CI: 1.01–1.40, P = 0.0412). Among various anti-tumor approaches, chemotherapy distinguished to increase the incidence of death (OR = 1.22, 95% CI: 1.08–1.38, P = 0.0013) and severe COVID-19 (OR = 1.10, 95% CI: 1.02–1.18, P = 0.0165) as to cancer patients with COVID-19. Moreover, for cancer patients with COVID-19, surgery and targeted therapy could add to the risk of death (OR = 1.27, 95% CI: 1.00–1.61, P = 0.0472), and the incidence of severe COVID-19 (OR = 1.14, 95% CI: 1.01–1.30, P = 0.0357) respectively. In the subgroup analysis, the incidence of death (OR = 1.17, 95% CI: 1.03–1.34, P = 0.0158) raised in case of chemotherapy adopted for solid tumor with COVID-19. Besides, age, gender, hypertension, COPD, smoking and lung cancer all served as potential prognostic factors for both death and severe disease of cancer patients with COVID-19.

Conclusions: Anti-tumor therapy, especially chemotherapy, augmented the risk of severe disease and death for cancer patients with COVID-19, so did surgery for the risk of death and targeted therapy for the incidence of severe COVID-19.

Keywords: Anti-tumor therapy, cancer, COVID-19, Chemotherapy, Solid tumor

Background

As is known to all, the sudden outbreak and global overrun of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) [1], have generated heavy burdens and great challenges to global public health since December...
2019 [2]. Up to date, people all over the world have been fighting against the fatal disease, as reported in over 200 million infected individuals.

Cancer patients are generally in severe immunosuppressive status deriving from cancer itself and the anti-tumor regimens. Furthermore, they have to visit the hospital regularly for monitoring or anti-tumor treatment (such as chemotherapy, immunotherapy, endocrine therapy, targeted therapy, surgery and radiotherapy) leading to increasing exposure to virus.

A growing number of studies revealed that, during the pandemic, cancer patients with COVID-19 generally suffered from worse outcomes compared to patients with COVID-19 alone [3–7]. In addition, some investigations targeted at exploring whether anti-tumor therapy was an additional risk factor for adverse outcomes of COVID-19 and whether it was necessary to change therapeutic modalities to mitigate the risk [8–10].

As far as we know, accumulating prospective and retrospective studies were conducted to evaluate clinical characteristics of cancer patients with COVID-19, as well as the impact of anti-tumor therapy on clinical outcomes of COVID-19 [11–13]. Nevertheless, research findings remained to be a bit conflicting and inconclusive as for the impact of anti-tumor therapeutic approaches on the severity of COVID-19 [14–18]. Consequently, a comprehensive survey based on a larger scale (52 cohorts incorporating 9231 individuals) and diverse dimensions was hereby carried out to clarify the correlation between anti-tumor therapy and COVID-19 prognosis.

**Methods**

**Data sources and literature searches**

A systematic electronic literature retrieval was in place for study screening, searching for abstracts of relevant studies in the published literature. PubMed, Cochrane Library and EMBASE were all searched with data updated as of 27th March 2021. Basic search terms entered were as follows: “COVID-19”, “SARS-CoV2”, “SARS-CoV-2”, “2019-nCoV”, “novel coronavirus”, “cancer”, “neoplasm”, “malignancy”, “carcinoma” and “tumor” (the full search strategy as shown in Additional file 1: Appendix 1). In addition, full-text papers were scrutinized as for abstracts without substantial information, and the references of relevant articles were reviewed for additional studies. Data retrieval was completed in English, with reviews, editorials comments and case reports all excluded.

**Selection of studies and definition**

Initially, two investigators performed a screening of titles and abstracts respectively, then examined the full-text of articles to acquire eligible studies. Regarding the duplicate studies based on the same patients, only the latest or most comprehensive data were recruited as a whole.

**Definition:**

- **Anti-tumor therapy:** patients receiving chemotherapy (cytotoxic chemotherapy), immunotherapy (immune checkpoint inhibitor), targeted therapy (molecular targeted therapy), surgery, radiotherapy, endocrine therapy (hormonal drugs) within the last 6 months before COVID-19 diagnosis.

- **Age:** defined as “old” or “young” depending on each cut-off used to calculate the odds ratios (ORs) of age in the included studies.

- **Eastern Cooperative Oncology Group Performance Scale (ECOG PS):** defined as “high” or “low” with a cut-off of 2.

- **Comorbidities:** defined as “yes” or “no” to identify cancer patients with or without hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, obesity status and smoking in the corresponding studies.

- **Blood parameters:** defined as “high” or “normal” on the basis of each cut-off applied to calculate the ORs of white blood cell count, C-reactive protein (CRP), lymphocyte count, D-dimer, neutrophil to lymphocyte ratio (NLR), and creatine kinase in each included study.

- **Severe COVID-19:** depending on respective definitions in the included studies, including infections requiring intensive care unit (ICU) admission, mechanical ventilation or even resulting in death.

**Inclusion criteria**

1) Prospective or retrospective studies to evaluate the impact of anti-tumor therapy on cancer patients with COVID-19; 2) patients pathologically confirmed as cancer; 3) patients diagnosed as COVID-19; 4) studies with data available for ORs and corresponding 95% confidence intervals (CIs) of severe COVID-19 and death rates in groups receiving anti-tumor treatments or not.

**Data extraction**

In this study, data extraction was implemented strictly according to the PRISMA guidelines (as shown in Additional file 2: Appendix 2). Meanwhile, all eligible studies involved the information as follows: the publication year and region, first author’s name, study type, number of patients, anti-tumor therapy, severe COVID-19 and/or death cases.

**Quality assessment**

The quality of included studies was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies,
encompassing three dimensions of selection, comparability and exposure, with a full score of 9 points.

Statistical methods
The primary endpoints were composed of death and/or severe COVID-19 of cancer patients treated with anti-tumor therapy before COVID-19 diagnosis. Moreover, the correlation between anti-tumor therapy and the outcomes was determined by ORs with the corresponding 95%CIs. Subgroup analyses were further accomplished based on the type of anti-tumor therapy, type of cancer (solid cancer or haematological malignancy) and other prognostic factors. In addition, funnel plots and Egger’s test were applied to evaluate publication bias, and statistical analysis was realized via R 4.0 statistical software. Heterogeneity was assessed by means of I-square tests and chi-square, with remarkable heterogeneity in case of $P < 0.1$ or $I^2 > 40$. Furthermore, a random effect model was adopted to analyze the pooled data when heterogeneity existed; otherwise, a fixed effect model was employed accordingly.

Results
Selection of study
Initially, 9462 relevant articles were scrutinized intensively, of which 443 were filtered for duplication, and 8766 were excluded for digression after screening the titles and abstracts. After that, the full text of remaining 253 articles was thoroughly reviewed, among which 201 were excluded as they were reviews or case reports, not human research, not in English, without data for ORs and corresponding 95%CIs of severe COVID-19 and/or death in groups receiving anti-tumor therapy or not. Finally, a total of 52 cohorts [4, 6, 7, 11, 12, 14–60] incorporating 9231 participants were recruited in this study. See Fig. 1 for detailed procedures.

Study traits
As of 27th March 2021, altogether 9231 individuals in 52 cohorts were included with a sample size ranging from 12 to 1289, of which 45 were retrospective, 4 prospective and 3 retro-prospective. Meanwhile, ORs for severe COVID-19 and/or death were utilized to assess the impact of anti-tumor approaches on cancer patients with COVID-19. Among the foregoing studies, 41 cohorts witnessed death and 23 confronted with severe COVID-19. See Table 1 for principal characteristics.

Assessment of study quality and publication bias
Refer to Additional file 3: Appendix 3 for quality assessment of 52 recruited studies. Furthermore, no publication bias was defined via Egger’s tests in the pooled analyses for various anti-tumor approaches (see Additional file 4: Appendix 4) and supernumerary prognostic factors (see Additional file 5: Appendix 5).

Data analysis
In this study, regarding cancer patients treated with anti-tumor therapy before COVID-19 diagnosis, the pooled OR was 1.21 (95%CI: 1.07–1.36, $P = 0.0026$) (Fig. 2A) for death without publication bias (Fig. 2C, Egger’s test: $P = 0.5516$), and 1.19 (95%CI: 1.01–1.40, $P = 0.0412$) (Fig. 2B) for severe COVID-19 without publication bias (Fig. 2D, Egger’s test: $P = 0.3930$).

The impact of anti-tumor therapy on death and severe disease of cancer patients with COVID-19
As for cancer patients with COVID-19, compared with patients without anti-tumor approaches, the incidence of death appeared to be higher in patients treated with chemotherapy (OR = 1.22, 95%CI: 1.08–1.38, $P = 0.0013$) (Fig. 3A) and surgery (OR = 1.27, 95%CI: 1.00–1.61, $P = 0.0472$) (Fig. 3B), but not in patients receiving radiotherapy (OR = 0.90, 95%CI: 0.75–1.09, $P = 0.2817$), targeted therapy (OR = 0.97, 95%CI: 0.76–1.23, $P = 0.7914$), endocrine therapy (OR = 0.95, 95%CI: 0.80–1.12, $P = 0.5097$), and immunotherapy (OR = 1.05, 95%CI: 0.90–1.22, $P = 0.5412$) (Additional file 6: Appendix 6).

Compared with cancer patients without anti-tumor approaches, the incidence of severe COVID-19 was higher in patients receiving chemotherapy (OR = 1.10, 95%CI: 1.02–1.18, $P = 0.0165$) (Fig. 3C) and targeted therapy (OR = 1.14, 95%CI: 1.01–1.30, $P = 0.0357$) (Fig. 3D), but not in patients treated with surgery (OR = 1.15, 95%CI: 0.89–1.47, $P = 0.2888$) and immunotherapy (OR = 1.18, 95%CI: 0.97–1.45, $P = 0.1034$) (Additional file 6: Appendix 6).

Subgroup analysis
Patients were further divided into groups of solid tumor and haematological malignancy depending on the type of cancer, as listed in Table 2. Compared with patients without anti-tumor approaches, solid tumor patients with COVID-19 witnessed higher incidence of death after receiving chemotherapy (OR = 1.17, 95%CI: 1.03–1.34, $P = 0.0158$), but not the case in haematological malignancy patients with COVID-19 (OR = 1.41, 95%CI: 0.74–2.68, $P = 0.2964$).

Supernumerary prognostic factors for death and severe disease of cancer patients with COVID-19
The potential prognostic factors for the death of cancer patients with COVID-19 were as follows: age
(OR = 1.15, 95% CI: 1.12–1.19, \( P < 0.0001 \)) (Fig. 4A), gender (OR = 1.22, 95% CI: 1.11–1.34, \( P < 0.0001 \)) (Fig. 4B), hypertension (OR = 1.32, 95% CI: 1.22–1.41, \( P < 0.0001 \)) (Fig. 4C), diabetes (OR = 1.31, 95% CI: 1.20–1.42, \( P < 0.0001 \)) (Fig. 4D), COPD (OR = 1.24, 95% CI: 1.08–1.41, \( P = 0.0016 \)) (Fig. 4E), cardiovascular disease (OR = 1.33, 95% CI: 1.15–1.55, \( P = 0.0001 \)) (Fig. 4F), smoking (OR = 1.29, 95% CI: 1.14–1.47, \( P < 0.0001 \)) (Fig. 4G), ECOG PS (OR = 1.73, 95% CI: 1.47–2.03, \( P < 0.0001 \)) (Fig. 4H), lung cancer (OR = 1.38, 95% CI: 1.05–1.81, \( P = 0.0200 \)) (Fig. 4I), white blood cell count (OR = 1.86, 95% CI: 1.17–2.97, \( P = 0.0093 \)) (Fig. 4J), and CRP (OR = 1.03, 95% CI: 1.00–1.05, \( P = 0.0298 \)) (Fig. 4K). Nevertheless, obesity status (OR = 1.02, 95% CI: 0.91–1.15, \( P = 0.6827 \)), lymphocyte count (OR = 1.24, 95% CI: 0.57–2.68, \( P = 0.5868 \)), D-dimer (OR = 1.01, 95% CI: 0.98–1.05, \( P = 0.3981 \)) and NLR (OR = 1.30, 95% CI: 0.64–2.64, \( P = 0.4763 \)) were not highly correlated to the death of cancer patients with COVID-19 (Additional file 7: Appendix 7).

Furthermore, the potential prognostic factors for severe disease of cancer patients with COVID-19 included age (OR = 1.10, 95% CI: 1.05–1.15, \( P < 0.0001 \)) (Fig. 5A), gender (OR = 1.12, 95% CI: 1.04–1.21, \( P = 0.0017 \)) (Fig. 5B), hypertension (OR = 1.22, 95% CI: 1.02–1.45, \( P = 0.0286 \)) (Fig. 5C), COPD (OR = 1.20, 95% CI: 1.01–1.43, \( P = 0.0416 \)) (Fig. 5D), smoking (OR = 1.21, 95% CI: 1.08–1.35, \( P = 0.0008 \)) (Fig. 5E), and lung cancer (OR = 1.30, 95% CI: 1.08–1.56, \( P = 0.0055 \)) (Fig. 5F). However,
| Author          | Year | Study design     | Region       | Number of patient | Male Median age (IQR) (years) | Diagnosis method for COVID-19 | Cancer type                                | Comparison group                                      |
|-----------------|------|------------------|--------------|-------------------|------------------------------|-------------------------------|--------------------------------------------|--------------------------------------------------------|
| Kuderer NM      | 2020 | Retro-prospective | multi-national | 928               | 468                          | 66 (57–76)                    | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Lee LYW         | 2020 | Prospective      | UK           | 800               | 449                          | 69 (59–76)                    | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Zhang L         | 2020 | Retrospective    | China        | 28                | 17                           | 65 (56–70)                    | RT-PCR                                    | solid tumor cancer patients with no treatment               |
| Stroppa EM      | 2020 | Retrospective    | Italy        | 25                | 20                           | 71 (mean) (50–84)             | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Yang K          | 2020 | Retrospective    | China        | 205               | 96                           | 63 (56–70)                    | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Zhang H         | 2020 | Retrospective    | China        | 107               | 60                           | 66 (36–98)                    | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Robilotti EV    | 2020 | Retrospective    | USA          | 423               | 212                          | NA                           | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Yarza R         | 2020 | Prospective      | Spain        | 63                | 34                           | NA                           | RT-PCR                                    | solid tumor cancer patients treated other options          |
| Li Q            | 2020 | Retrospective    | China        | 59                | 31                           | 63 (54–70)                    | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Jee J           | 2020 | Retrospective    | USA          | 309               | 159                          | NA                           | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Sanchez-Pina JM | 2020 | Retrospective    | Spain        | 39                | 23                           | 64 (mean)                     | RT-PCR                                    | hematological malignancies cancer patients with no treatment |
| Pinato DJ       | 2020 | Retrospective    | multi-national | 890            | 503                           | 68 (mean)                     | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Assaad S        | 2020 | Retrospective    | France       | 55                | 26                           | 64 (mean)                     | RT-PCR                                    | non-specific cancer patients with no treatment               |
| Study       | Year | Design      | Country     | N  | Treatment | Test Method                                      | Cancer Type                  | Notes                                                                 |
|------------|------|-------------|-------------|----|-----------|------------------------------------------------|-----------------------------|----------------------------------------------------------------------|
| Garassino MC [28] | 2020 | Retrospective | multi-national | 200 | 141       | 68 (61–75)  RT-PCR                              | Thoracic Cancer             | cancer patients with no treatment                                     |
| Liang WH [29]  | 2020 | Retrospective | China       | 18  | 12        | 60 (47–87)  RT-PCR                              | non-specific                | cancer patients with no treatment                                     |
| Ma J [30]  | 2020 | Retrospective | China       | 37  | 20        | 62 (IQR: 59–70) RT-PCR and/or antibody test     | solid tumor                 | cancer patients with no treatment                                     |
| Mehta V [11]  | 2020 | Retrospective | USA         | 218 | 127       | 69 (10–92)  RT-PCR                              | non-specific                | cancer patients with no treatment                                     |
| Yu J [31]  | 2020 | Retrospective | China       | 12  | 10        | 66 (48–78)  RT-PCR and/or CT                     | solid tumor                 | cancer patients with no treatment                                     |
| Tian J [4]  | 2020 | Retrospective | China       | 232 | 119       | 64 (58–69)  RT-PCR                              | non-specific                | cancer patients with no treatment                                     |
| Fox TA [32]  | 2020 | Retrospective | UK          | 55  | 38        | 63 (23–88)  RT-PCR, CT, and clinical features   | hematological malignancies  | cancer patients with no treatment                                     |
| Booth S [33]  | 2020 | Prospective  | UK          | 66  | 41        | 73 (IQR: 63–81) RT-PCR, radiological, and clinical features | hematological malignancies  | cancer patients with no treatment                                     |
| Cattaneo C [34]  | 2020 | Retrospective | Italy       | 102 | 66        | 68 (mean)  RT-PCR                              | hematological malignancies  | cancer patients with no treatment                                     |
| Lara OD [35]  | 2020 | Retrospective | USA         | 121 | NA        | 64 (IQR: 51–73) RT-PCR and CT                   | gynecologic cancer          | cancer patients with no treatment                                     |
| Liu C [36]  | 2020 | Retrospective | China       | 216 | 113       | 63 (IQR: 57–70) RT-PCR                          | solid tumor                 | cancer patients with no treatment                                     |
| Luo J [37]  | 2020 | Retrospective | USA         | 102 | 49        | 68 (IQR: 61–75) RT-PCR                          | lung cancer                 | cancer patients with no treatment                                     |
Table 1 (continued)

| Authors            | Year | Study Type | Country/Region | Cohort Size | Age Range | Diagnostic Test | Tumor Type          | Treatment Status                      |
|--------------------|------|------------|----------------|-------------|------------|-----------------|---------------------|----------------------------------------|
| Mato AR [38]       | 2020 | Retrospective | multi-national | 198        | 63 (35–92) | RT-PCR          | chronic lymphocytic leukemia | cancer patients with no treatment |
| Rogado J [39]      | 2020 | Retrospective | Spain          | 45         | 71 (34–90) | RT-PCR          | non-specific          | cancer patients with no treatment |
| Russell B [40]     | 2020 | Retrospective | UK             | 156        | 65 (mean)  | RT-PCR          | solid tumor          | cancer patients with no treatment |
| Scarfo L [41]      | 2020 | Retrospective | multi-national | 190        | 72 (48–94) | RT-PCR          | chronic lymphocytic leukemia | cancer patients with no treatment |
| Vuagnat P [42]     | 2020 | Retrospective | France         | 58         | 58 (IQR: 48–68) | RT-PCR and/or CT | breast cancer | cancer patients with no treatment |
| Wang BO [43]       | 2020 | Retrospective | USA            | 58         | 67         | RT-PCR          | multiple myeloma     | cancer patients with no treatment |
| Wang J [44]        | 2020 | Retrospective | China          | 283        | 63 (IQR: 55–70) | RT-PCR          | non-specific          | cancer patients with no treatment |
| Gonzalez-Cao M [45]| 2020 | Retrospective | Spain          | 50         | 69 (6–94)  | clinical or RT-PCR | melanoma           | cancer patients with no treatment |
| De Melo AC [46]    | 2020 | Retrospective | Brazil         | 181        | 55 (2–88)  | RT-PCR          | non-specific          | cancer patients with no treatment |
| Albiges L [47]     | 2020 | Retrospective | France         | 178        | 61 (52–71) | RT-PCR and/or CT | non-specific          | cancer patients with no treatment |
| Martinez-Lopez J [48]| 2020 | Retrospective | Spain          | 167        | 71 (IQR: 62–78) | RT-PCR          | multiple myeloma (MM) | cancer patients with no treatment |
| Martin-Moro F [49] | 2020 | Retrospective | Spain          | 34         | 72.5 (35–94) | RT-PCR and/or CT | hematological malignancies | cancer patients with no treatment |
| Lattenist R [50]   | 2021 | Retrospective | Belgium        | 13         | 70 (IQR: 59–79) | RT-PCR and/or CT | hematological malignancies | cancer patients with no treatment |
| Study | Year | Study Design | Country | Age | Patients | Test Method | Cancer Type | Treatment Status |
|-------|------|--------------|---------|-----|----------|-------------|-------------|-----------------|
| Nakamura S [51] | 2020 | Retrospective | Japan | 32-22 | 745 (24-90) | RT-PCR | non-specific cancer patients with no treatment |
| Rogiers A [52] | 2021 | Retrospective | multi-national | 110-72 | 63 (27-86) | RT-PCR | non-specific cancer patients with no treatment |
| Glenthøj A [16] | 2021 | Prospective | Denmark | 66-40 | 667 (25-91) | hematological malignancies | cancer patients with no treatment |
| Song C [17] | 2020 | Retrospective | China | 223-116 | 63 (56-71) | RT-PCR | non-specific cancer patients with discontinuous treatment |
| Lunski MJ | 2020 | Retrospective | USA | 312-142 | NA | RT-PCR | non-specific cancer patients with no treatment |
| Nie L [53] | 2020 | Retrospective | China | 45-31 | 66 (58-74) | RT-PCR | lung cancer cancer patients with no treatment |
| Larfor G [54] | 2020 | Retrospective | Sweden | NA-NA | NA | RT-PCR | non-specific cancer patients with no treatment |
| Høglein A [55] | 2020 | Retrospective | Germany | 17-8 | 73 (27-82) | RT-PCR | non-specific cancer patients with no treatment |
| Garnett C [56] | 2020 | Retrospective | UK | 32-21 | 725 (46-96) | RT-PCR | hematological malignancies cancer patients with no treatment |
| Hanna GJ | 2020 | Retrospective | USA | 32-20 | 70 (38-91) | RT-PCR | head and neck cancer cancer patients with no treatment |
| Lie'vre A [58] | 2020 | Retrospective | France | 1289-795 | 67 (19-100) | RT-PCR | solid tumor cancer patients with no treatment |
| Smith M [59] | 2020 | Retrospective | USA | 86-NA | 69 (mean) | RT-PCR | solid tumor cancer patients with no treatment |
| Wu YG [60] | 2020 | Retrospective | China | 14-9 | 37 (14-68) | RT-PCR | hematological malignancies cancer patients with no treatment |
| Yang F [12] | 2020 | Retrospective | China | 52-28 | 63 (34-98) | RT-PCR | solid tumor cancer patients with no treatment |
| Author        | Number of the control | Anti-tumor therapy | Chemotherapy | Immunotherapy | Targeted therapy | Endocrine therapy | Surgery | Radiotherapy | Outcome        | Required mechanical ventilation | Severe COVID-19 | Death |
|---------------|------------------------|--------------------|--------------|---------------|------------------|-------------------|---------|--------------|-----------------|-------------------------------|----------------|-------|
| Kuderer NM    | 553                    | 366                | 160          | 38            | 75               | 85                | 32      | 12           | death           | 116                           | 242            | 121   |
| Lee LYW       | 272                    | 528                | 281          | 44            | 72               | 64                | 29      | 76           | death           | NA                           | 360            | 226   |
| Zhang L       | 22                     | 6                  | 3            | 1             | 2                | NA                | NA      | 1            | severe COVID-19 | death                        | 15             | 8     |
| Stroppa EM    | 13                     | 12                 | 8            | 4             | NA               | NA                | NA      | NA           | death           | NA                           | NA             | 9     |
| Yang K        | 128                    | 54                 | 31           | 4             | 12               | NA                | NA      | 4            | 9               | death                        | 32             | 40    |
| Zhang H       | 70                     | 37                 | NA           | 6             | NA               | NA                | NA      | NA           | death           | NA                           | 52             | 40    |
| Robiotoli EV  | NA                     | NA                 | 191          | 31            | NA               | NA                | NA      | 31           | death           | NA                           | NA             | 40    |
| Yarza R       | NA                     | NA                 | 36           | 8             | 7                | 10                | NA      | NA           | sever COVID-19 | NA                           | 85             | 51    |
| Li Q          | 43                     | 16                 | 12           | NA            | 6                | NA                | 1       | 1            | death           | 27                           | 35             | 16    |
| Jee J         | 43                     | 170                | 102          | 18            | 49               | NA                | NA      | NA           | death           | NA                           | 120            | 31    |
| Sanchez-Pina JM | 15             | 24                 | 4            | NA            | 5                | NA                | NA      | NA           | death           | NA                           | 18             | NA    |
| Pinato DJ     | 403                    | 479                | 206          | 56            | 93               | 92                | NA      | 33           | sever COVID-19 | 97                           | 565            | 299   |
| Assaad S      | 26                     | 29                 | 16           | 3             | 14               | NA                | NA      | NA           | death           | NA                           | NA             | 30    |
| Garassino MC  | 58                     | 142                | 48           | 34            | 28               | NA                | NA      | NA           | death           | 9                            | NA             | 66    |
| Liang WH      | 14                     | 4                  | NA           | NA            | NA               | NA                | NA      | NA           | death           | NA                           | NA             | 9     |
| Maj [30]      | 24                     | 13                 | NA           | NA            | NA               | NA                | NA      | NA           | sever COVID-19 | death                        | 20             | 5     |
| Mehta V       | NA                     | NA                 | 42           | 5             | NA               | NA                | NA      | 49           | death           | NA                           | NA             | 61    |
| Yu J [31]     | 5                      | 7                  | 5            | 2             | 1                | NA                | 1       | 4            | sever COVID-19 | death                        | NA             | 3     |

Note: Table 1 (continued)
| Author            | Age | Gender | Race | BMI | HTN | DM | COPD | COVID-19 Description | Other Conditions | Other Notes |
|-------------------|-----|--------|------|-----|-----|----|------|----------------------|-----------------|------------|
| Tian J [4]        | NA  | NA     | NA   | NA  | NA  | NA | 119  | NA                   | NA              | 148        |
| Fox TA [32]       | NA  | NA     | 29   | 25  | NA  | NA | NA   | NA                   | NA              | 25         |
| Booth S [33]      | 29  | 37     | NA   | NA  | NA  | NA | NA   | NA                   | NA              | 148        |
| Cattaneo C [34]   | 43  | 59     | 20   | 28  | NA  | NA | NA   | death NA             | NA              | 25         |
| Lara OD [35]      | NA  | NA     | NA   | NA  | NA  | NA | NA   | death NA             | NA              | 20         |
| Liu C [36]        | 138 | 78     | NA   | NA  | NA  | NA | NA   | death NA             | NA              | 37         |
| Luo J [37]        | 48  | 54     | NA   | NA  | NA  | NA | NA   | NA                   | NA              | 25         |
| Mato AR [38]      | 79  | 119    | 51   | NA  | NA  | NA | NA   | death 53             | NA              | 66         |
| Rogado J [39]     | 15  | 30     | 19   | 1   | 2   | NA | NA   | death NA             | NA              | 29         |
| Russell B [40]    | 18  | 81     | 45   | 7   | 5   | NA | NA   | death NA             | NA              | 28         |
| Scarfò L [41]     | 73  | 116    | NA   | NA  | NA  | NA | NA   | death NA             | NA              | 151        |
| Vuagnat P [42]    | NA  | NA     | 29   | NA  | 19  | 19 | 3    | 36                   | NA              | 4          |
| Wang BO [43]      | 11  | 47     | NA   | NA  | 28  | NA | NA   | death NA             | NA              | 14         |
| Wang J [44]       | 188 | 95     | 46   | NA  | 12  | NA | 23   | NA                   | NA              | 50         |
| Gonzalez-cao M [45]| 12  | 38     | NA   | 22  | 16  | NA | NA   | NA                   | NA              | 34         |
| De Melo AC [46]   | 16  | 165    | 63   | NA  | NA  | 20 | 12   | 10                   | NA              | 60         |
| Albiges L [47]    | 61  | 117    | 66   | 19  | 30  | 16 | NA   | NA                   | NA              | 47         |
| Martinez-López J [48]| NA  | NA     | 83   | NA  | NA  | NA | NA   | death 15             | NA              | 141        |
Table 1 (continued)

|                | ICIs | Age | RT-PCR | ICIs | Age | RT-PCR | ICIs | Age | RT-PCR | ICIs | Age | RT-PCR | ICIs | Age | RT-PCR | ICIs | Age | RT-PCR | ICIs | Age | RT-PCR |
|----------------|------|-----|--------|------|-----|--------|------|-----|--------|------|-----|--------|------|-----|--------|------|-----|--------|------|-----|--------|
| Wu et al.      | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Lattenist      | 6    | 7   | 3      | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Nakamura       | 13   | 10  | 3      | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Rogiers        | NA   | NA  | 25     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Glenthøj       | 10   | 9   | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Song           | 19   | 204 | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Lunski MJ      | 256  | 56  | 12     | 4    | 9   | 44     | 5    | 2   | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Nie L          | 34   | 11  | 4      | 4    | NA   | NA     | 3    | NA  | death  | 3    | NA  | 11     | NA   | 11  | NA     | NA   | 11  | NA     | NA   | 11  | NA     |
| Larfors        | NA   | NA  | NA     | NA   | NA  | NA     | NA   | NA  | NA     | NA   | NA  | NA     | NA   | NA  | NA     | NA   | NA  | NA     | NA   | NA  | NA     |
| Hkollein A     | 2    | 15  | 14     | 1    | 2   | NA     | NA   | 1   | death  | 3    | NA  | 6      | NA   | 6   | NA     | NA   | 6   | NA     | NA   | 6   | NA     |
| Garnett C      | 10   | 22  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Hanna GJ       | 26   | 6   | 3      | 1    | 0   | NA     | 4    | 1   | death  | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Lie've A       | NA   | NA  | 577    | 110  | 181 | 57     | 56   | 133 | death  | 49   | NA  | 370    | NA   | 370 | NA     | NA   | 370 | NA     | NA   | 370 | NA     |
| Smith M        | 47   | 39  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Wu YG          | NA   | NA  | 7      | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     | NA   | 19  | NA     |
| Yang F         | NA   | NA  | 6      | 1    | NA  | NA     | NA   | 2   | NA     | NA   | 2   | NA     | NA   | 2   | NA     | NA   | 2   | NA     | NA   | 2   | NA     |

Abbreviations: ICIs Immune checkpoint inhibitors, RT-PCR Reverse transcription-polymerase chain reaction, NA Not available, ICU Intensive Care Unit
such factors as diabetes (OR = 1.03, 95%CI: 0.88–1.20, P = 0.7415), obesity status (OR = 1.00, 95%CI: 0.92–1.10, P = 0.9254), ECOG PS (OR = 1.39, 95%CI: 0.93–2.07, P = 0.1119), white blood cell count (OR = 0.33–2.07, P = 0.1119), lymphocyte count (OR = 0.77–2.50, P = 0.1196), CRP (OR = 1.39, 95%CI: 0.77–2.50, P = 0.1119), D-dimer (OR = 1.02, 95%CI: 0.76–1.36, P = 0.9093), and creatine kinase (OR = 1.05, 95%CI: 0.90–1.20, P = 0.1387) did not obviously influence the severe disease of cancer patients with COVID-19 (Additional file 7: Appendix 7).

Subgroup analysis

Depending on the type of cancer, patients were further assigned into groups of solid tumor and hematological malignancy, as listed in Additional file 8: Appendix 8.

Fig. 2. The impact of anti-tumor therapy on clinical outcomes of cancer patients with COVID-19. Forest plots of (A) death, (B) severe COVID-19 between groups divided by receiving anti-tumor therapy or not before COVID-19 diagnosis (Additional file 7: Appendix 7).
Fig. 3 The impact of various anti-tumor approaches on clinical outcomes of cancer patients with COVID-19. The impact of (A) chemotherapy and (B) surgery on death of cancer patients with COVID-19; The impact of (C) chemotherapy and (D) targeted therapy on severe disease of cancer patients with COVID-19.

Table 2 Subgroup analysis of the impact of anti-tumor therapy on death and severe disease of cancer patients with COVID-19

| Anti-tumor therapy | Solid tumour | Haematological malignancy |
|--------------------|--------------|---------------------------|
|                    | death        | severe COVID-19           | death                      | severe COVID-19 |
|                    | OR (95%CI)   | P                         | OR (95%CI)                | P                | OR (95%CI)     | P                | OR (95%CI)     | P                |
| Chemotherapy       | 1.17 (1.03–1.34) | 0.0158                  | 1.16 (0.81–1.66)  | 0.4072          | 1.41 (0.74–2.68)  | 0.2964          | NA              | NA                |
| Radiotherapy       | NA           | NA                        | NA                       | NA               | NA              | NA               | NA              | NA                |
| Targeted therapy   | NA           | NA                        | NA                       | NA               | NA              | NA               | NA              | NA                |
| Surgery            | NA           | NA                        | NA                       | NA               | NA              | NA               | NA              | NA                |
| Endocrine therapy  | NA           | NA                        | NA                       | NA               | NA              | NA               | NA              | NA                |
| Immunotherapy      | 0.91 (0.47–1.76) | 0.7705                  | NA                       | NA               | NA              | NA               | NA              | NA                |
| Antitumor therapy  | 1.15 (0.94–1.42) | 0.1815                  | 1.08 (0.88–1.32)  | 0.4643          | 1.26 (0.91–1.75)  | 0.1597          | NA              | NA                |

Abbreviations: NA, Not available; OR, Odds ratio; CI, Confidence interval.
The potential prognostic factors for the death of solid tumor patients with COVID-19 included age (OR = 1.01, 95%CI: 1.00–1.01, $P = 0.0168$), gender (OR = 1.22, 95%CI: 1.09–1.36, $P = 0.0006$), hypertension (OR = 1.20, 95%CI: 1.01–1.42, $P = 0.0446$), and smoking (OR = 1.19, 95%CI: 1.04–1.35, $P = 0.0110$).

Furthermore, age (OR = 1.37, 95%CI: 1.20–1.57, $P < 0.0001$), hypertension (OR = 1.20, 95%CI: 1.02–1.41, $P = 0.0246$) and diabetes (OR = 1.26, 95%CI: 1.03–1.53, $P = 0.0245$) ranked as the potential prognostic factors for the death of haematological malignancy patients with COVID-19.

Discussion

A meta-analysis involving 15 studies demonstrated that chemotherapy could increase the risk of death from COVID-19 in cancer patients [61]. To our best knowledge, this study composed of 52 cohorts involving 9231 cancer patients with COVID-19, was so far the largest-scale investigation with respect to the impact of anti-tumor approaches on clinical outcomes of cancer patients with COVID-19, indicating that cancer patients with recent anti-tumor therapy (especially chemotherapy) were generally susceptible to develop into severe COVID-19, or even death.

Firstly, cancer patients with COVID-19 receiving chemotherapy were more likely to confront with severe disease and death, probably because patients treated with chemotherapy were susceptible to suffer from bone marrow suppression (including severe neutropenia or lymphocytopenia) and impaired immunity [62, 63], even respiratory infections (involving viral etiology) [64]. Furthermore, the recovery of immune system might take a long time after the weakening of immune functions by chemotherapy [65]. As a result, cancer patients with COVID-19 failed to effectively activate the immune system to eliminate the virus in a timely manner [66], that's why they were more likely to trigger severe disease or even death.

Secondly, recent surgery might lead to increasing risk of death and a trend of severe disease in cancer patients with COVID-19, partially attributable to their frequent visits to hospital and postoperative negative nitrogen balance. Moreover, the stress and trauma caused by surgery could be clinically manifested as decreased immunity, since numerous studies revealed that the immunity of patients would reduce to a certain extent in a period of time after surgery [67].

Thirdly, patients administered with targeted therapy before COVID-19 diagnosis faced with elevated risk of severe disease. Despite targeted therapy seldomly impaired the immunity system of cancer patients, all those receiving maintenance targeted therapy suffered from advanced disease and many complications in general, giving rise to clinical worsening as a result.

Finally, tumor immunotherapy has played an increasingly crucial role in the field of anti-tumor treatment over the past decade [68]. As shown in our study, cancer patients with COVID-19 who received immunotherapy recently did not generate a higher rate of severe disease or death when comparing to those without immunotherapy.

In summary, this study aimed at providing clinicians with preliminary evidence for the safety of anti-tumor approaches during COVID-19. As to patients with COVID-19 who received anti-tumor approaches recently, especially chemotherapy, surgery and targeted therapy, clinicians should focus on disease progression and make intervention in a timely manner when necessary. Furthermore, intensive nursing and positive measures shall be taken to improve the prognosis and reduce the risk of death in practice.

Limitations

This study came up with four drawbacks as follows: firstly, limited studies related to radiotherapy, surgery and endocrine therapy might affect the accuracy of pooled results to some degree; secondly, 23 included studies failed to separate solid tumor from haematological malignancy for investigating the impact of anti-tumor approaches on the clinical outcomes, which might influence the accuracy of results; thirdly, bias might exist to some extent for excluding relevant studies published in non-English language; lastly, other forms of bias should be taken into account as follows: position bias (e.g. different health care systems and national policies in managing COVID-19) and time lag bias (time of study: start of pandemic vs. later phase of pandemic), which were not available in the included studies.
Fig. 4 (See legend on previous page.)
Conclusions

Anti-tumor therapy, especially chemotherapy, augmented the risk of severe disease and death for cancer patients with COVID-19, so did surgery for the risk of death and targeted therapy for the incidence of severe COVID-19.

Abbreviations

COVID-19: Coronavirus disease 2019; ORs: Odds ratios; CIs: Confidence intervals; COPD: Chronic obstructive pulmonary disease; SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus 2; NOS: Newcastle-Ottawa Scale; ECOG PS: Eastern Cooperative Oncology Group Performance Scale; NLR: Neutrophil to lymphocyte ratio; ICIs: Immune checkpoint inhibitors; T-PCR: Reverse transcription-polymerase chain reaction; NA: Not available; ICU: Intensive care unit.
Supplementary Information

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Additional file 1.
Additional file 2.
Additional file 3.
Additional file 4.
Additional file 5.
Additional file 6.
Additional file 7.
Additional file 8.

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Code availability
Not applicable.

Registration and protocol
The review was not registered and the protocol was not prepared.

Authors’ contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Qing Wu, Shuimei Luo and Xianhe Xie. The first draft of manuscript was written by Qing Wu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

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Consent for publication
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Competing interests
The authors declare no competing interests.

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