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Does prior exposure to immune checkpoint inhibitors treatment affect incidence and mortality of COVID-19 among the cancer patients: The systematic review and meta-analysis

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\textbf{ABSTRACT}

\textit{Background:} Immune checkpoint inhibitors (ICIs) treatment among cancer patients has been shown to have antiviral effects by reactivating exhausted T cells. However, they could also trigger inflammatory storm. Therefore, prior exposure to ICIs may influence the risk of SARS-CoV2 infection and subsequent mortality. Recent results from studies of ICIs treatment on incidence and mortality of COVID-19 are controversial.

\textit{Materials and methods:} We searched databases PubMed, Embase, ISI of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL), as well as pre-print databases (MedRxiv and BioRxiv) for retrospective and prospective studies comparing ICIs versus other antitumor treatments in cancer patients in the area of COVID-19 pandemic. The primary outcome was the incidence of COVID-19. The secondary outcomes were mortality of COVID-19 infection.

\textit{Results:} Twenty-three studies with a total of 117,735 patients were selected. Compared with other antitumor treatments, prior exposure to ICIs had not an increased risk of incidence [Odds ratio (OR), 0.84; 95\% confidence interval (CI), 0.60–1.18; \(P = 0.32\)] and mortality (OR, 1.22; 95\% CI, 0.91–1.62; \(P = 0.18\)) of COVID-19 infection. Our subgroup and meta-regression analyses indicated that prior exposure to ICIs may reduce the incidence of COVID-19 in metastatic cancer patients.

\textit{Conclusions:} There was no significant difference on incidence and mortality of COVID-19 between prior exposure to ICIs with other anti-tumor treatments. ICIs may reduce infection susceptibility of COVID-19 in metastatic cancer patients.

1. \textbf{Introduction}

The Coronavirus Disease 2019 (COVID-19) pandemic spread globally since 11 March 2020, and patients with cancer are more likely to suffer from COVID-19 infection and are thought to have a higher risk of adverse events than those without cancer [1]. The incidence of COVID-19 ranges from 0.5 to 6\%, and the mortality is approximately 25.0\% in patients with cancer [2–5].

Immunopathological findings of COVID-19 are characterized by apoptosis of sensitized T-cell and delay of IFN production[6]. During COVID-19 progression, functional impairment of CD4 + T lymphocytes and exhaustion of CD8 + cytotoxic T lymphocytes may lead to lower humoral and cellular immunity against viral infections[7–9]. In the early phase of COVID-19 infection, the increased expression of programmed cell death-1/programmed death-Ligand-1 (PD-1/PD-L1) in the surface of circulating T cells may represent a marker of T-cell exhaustion[10]. Immune checkpoint inhibitors (ICIs), specifically those targeting PD-1/PD-L1, serve to activate an anti-tumor response in the...
Table 1

Summarized Study Design of Included Trials.

| Study          | Country     | Study Design | Recruitment period | Control                                                                 | Sample size | Diagnostic method of COVID-19                                                                 | The time of anti-cancer treatment before COVID-19 diagnosis | Clinical End Point |
|---------------|-------------|--------------|--------------------|-------------------------------------------------------------------------|-------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------------|
| Justin Jee    | USA         | Retrospective, Single center | March 8, 2020 to June 2, 2020 | No ICI treatment                                                       | 154         | A nasopharyngeal swab and RT-PCR assay                                                       | Within 90 days prior to SARS-CoV-2 diagnosis                | Mortality         |
| Lennard YW    | UK          | Prospective, Multi center | March 18, 2020 to April 26, 2020 | Chemotherapy, hormonotherapy, radiotherapy, surgery, targeted treatment | 800         | A nose or throat swab and RT-PCR assay                                                       | Cancer treatment within 4 weeks of COVID-19 diagnosis       | Mortality         |
| Mario Mandala | Italy       | Prospective, Single center | March 5, 2020 to May 18, 2020 | Chemotherapy, targeted treatment                                       | 293         | A nasopharyngeal swab and RT-PCR assay for IgM/IgG seropositivity                           | Cancer treatment within 3 months of COVID-19 diagnosis       | Incidence and mortality |
| Nikolai Klebano | USA     | Retrospective, Single center | July 1, 2019, to February 29, 2020 | No ICI treatment                                                       | 21,963      | RT-PCR or a positive serology test and symptoms or known exposure                            | NA                                                         | Incidence and mortality |
| Marina Chiara Garassino | Italy    | Retrospective, Multi center | March 26, 2020 to April 12, 2020 | Chemotherapy, targeted treatment, other treatment                     | 200         | RT-PCR or suspected COVID-19 with symptoms                                                   | Within a median of 7 days (IQR 0–17) before COVID-19 diagnosis | Mortality         |
| Maria Antonietta Isgrò | Italy    | Retrospective, Single center | March 30, 2020 to May 15, 2020 | Chemotherapy                                                           | 885         | SARS-CoV-2 Immunoglobulins IgG and IgM                                                        | NA                                                         | Incidence         |
| Aljoja Rogiers | Australia   | Retrospective, Multi center | March 5, 2020 to May 15, 2020 | Chemotherapy                                                           | 110         | RT-PCR or a positive serology test                                                           | Within 12 months prior to COVID-19 diagnosis                | Mortality         |
| Jia Luo       | USA         | Retrospective, Single center | March 12, 2020 to April 13, 2020 | No ICI treatment                                                       | 69          | RT-PCR                                                                                      | NA                                                         | Mortality         |
| Maria Gonzalez-Cao | Spain   | Prospective, Single center | April 1, 2020 to June 8, 2020 | Targeted treatment, no treatment                                       | 70          | NA                                                                                          | NA                                                         | Incidence and mortality |
| Mengyuan Dai  | China       | Retrospective, Multi center | January 1, 2020 to Feb 24, 2020 | Chemotherapy, radiotherapy, surgery, targeted treatment               | 105         | According to the WHO interim guidance with the onset of COVID-19 symptoms                   | NA                                                         | Mortality         |

(continued on next page)
The influence of immune checkpoint inhibitors (ICIs) on the risk of COVID-19 infection and subsequent mortality has been a topic of interest. ICIs, which include drugs such as anti-PD-1 and anti-PD-L1 antibodies, are used to treat cancer patients by inhibiting immune evasion in cancer cells and restarting the proliferation of both B and T cells, thereby increasing cytokine secretion and retranslating the impairment of immune function.[17] Cancer patients treated with ICIs have been demonstrated to be able to restore their immunocompetence during HIV, hepatitis B, or hepatitis C viral infection, suggesting that ICIs have a potential antiviral effect.[15] Also the immune-related adverse events (irAEs) including myocarditis or pneumonitis indicate the immune and cytokine activation during the treatment of ICIs, which is similar with the pathological features in the progression of COVID-19.[7,16]. These findings support the possibility that ICIs may counteract the immunologic impairment of T-cell number and function, thereby resulting in a beneficial effect for COVID-19. However, the significant inflammatory damage may be exacerbated by anti-PD-1/PD-L1 during the late period of the disease.[17]. The use of ICIs in cancer patients may influence the risk of COVID-19 infection and subsequent mortality.[18–20]. However, data remains unclear regarding incidence and mortality associated with COVID-19 in cancer patients receiving ICIs treatment.[21–23]. Hence, we conducted a meta-analyses to evaluate the effects of ICIs treatment on the incidences and morality of COVID-19 in cancer patients.

### 2. Material and methods

#### 2.1. Search strategy and study criteria

This meta-analyses was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[24]. We did a systematic search using Medical Subject Headings (MeSH) and keywords in the following electronic bibliographic databases: PubMed, Embase, ISI of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL), as well as pre-print databases (MedRxiv and BioRxiv) from inception until May 2021. In the case of duplicate records of a single study, we will consider the PubMed database to take precedence. A full electronic search strategy for the management of many solid cancers and hematological malignancies[11–13]. PD-1 and PD-L1 are expressed both on tumor cells and on immune cells such as T and B cells, monocytes, dendritic cells (DCs), natural killer (NK) and NK T cells. Blockade of PD-1 to PD-L1 not only inhibits the immune evasion in cancer cell, but also restarts the proliferation of both B and T cells, increases cytokine secretion, and renovates the impairment of immune function[14]. Cancer patients treated with ICIs have been demonstrated to be able to restore their immunocompetence during HIV, hepatitis B, or hepatitis C viral infection, suggesting that ICIs have a potential antiviral effect[15]. Also the immune-related adverse events (irAEs) including myocarditis or pneumonitis indicate the immune and cytokine activation during the treatment of ICIs, which is similar with the pathological features in the progression of COVID-19[7,16]. These findings support the possibility that ICIs may counteract the immunologic impairment of T-cell number and function, thereby resulting in a beneficial effect for COVID-19. However, the significant inflammatory damage may be exacerbated by anti-PD-1/PD-L1 during the late period of the disease[17]. The use of ICIs in cancer patients may influence the risk of COVID-19 infection and subsequent mortality[18–20]. However, data remains unclear regarding incidence and mortality associated with COVID-19 in cancer patients receiving ICIs treatment[21–23]. Hence, we conducted a meta-analyses to evaluate the effects of ICIs treatment on the incidences and morality of COVID-19 in cancer patients.

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Table 2
Summarized patient characteristic of the included trials.

| Study                  | Age | Male (%) | DM (%) | HP (%) | COPD (%) | HF (%) | Smoke history (%) | Kidney disease (%) | ACEI/ARB (%) | Hormone (%) | Lung cancer (%) | Solid tumor (%) | Metastatic tumor (%) | MV (%) | ICU (%) | Hospital (%) |
|------------------------|-----|----------|--------|--------|----------|--------|-------------------|-------------------|--------------|-------------|-----------------|------------------|-----------------------|--------|---------|-------------|
| Justin Jee             | NA  | 48.3     | NA     | NA     | NA       | NA     | 38.2              | NA                | 3.7          | 9           | NA             | NA               | NA                    | NA     | NA      | NA          |
| Lennard YW Lee         | 69  | 56       | 16     | 31     | 8        | 14     | NA                | NA                | NA           | NA          | NA             | 11               | NA                    | 43     | NA      | 7           |
| Mariomandala           | 66.5| 67.3     | 25     | NA     | 27.3     | 80.7   | NA                | NA                | 8            | NA          | NA             | NA               | NA                    | NA     | NA      | 3.4         |
| NikolaiKlebanov        | 66.6| 58.1     | 16.4   | 53.2   | 24.1     | 10.7   | NA                | NA                | 15.6         | NA          | NA             | NA               | NA                    | NA     | NA      | NA          |
| MarinaChiara Garassino | 68  | 70       | 15     | 47     | 26       | 15     | 81                | NA                | 28           | 22          | 91             | NA               | 74                    | 6      | 9       | 76          |
| Maria Antonietta Igro  | 68  | 59       | NA     | NA     | NA       | NA     | NA                | NA                | NA           | NA          | NA             | NA               | NA                    | NA     | NA      | NA          |
| Aljosja Rogiers        | 63  | 65       | 15     | NA     | 12       | 27     | NA                | NA                | 5            | NA          | NA             | NA               | 16                    | NA     | 3       | 32          |
| Jia Loo                | 69  | 48       | 30     | 55     | 17       | 7      | NA                | NA                | NA           | NA          | NA             | NA               | NA                    | NA     | 20      | 23          |
| Maria Gonzalez-Cao     | 68  | 59       | NA     | NA     | NA       | NA     | NA                | NA                | NA           | NA          | NA             | NA               | 0                     | NA     | 6       | 70          |
| Mengyuan Dai           | 64  | 54.7     | 6.7    | 28.6   | 8.6      | 16.2   | 34.3              | NA                | 5.7          | NA          | 21.0          | NA               | 16.2                  | 58.1   | NA      | NA          |
| Vikas Mehta            | 68.8| 58.3     | 37.7   | 67.4   | 28.4     | 34.9   | NA                | NA                | 24.8         | NA          | NA             | NA               | NA                    | 19.3   | 20.6    | 10.6        |
| Kunya Yang             | 63  | 47       | 11     | 33     | 2        | 8      | 2                 | NA                | NA           | NA          | 12            | 89               | NA                    | 16     | 15      | NA          |
| David J. Pinato        | 68  | 56.5     | 20.3   | 43     | NA       | 21.3   | NA                | NA                | 4.7          | NA          | 84.6          | 43.8             | 10.9                  | NA     | 85.4    | NA          |
| Valerie E. Crolley     | 64  | 48.1     | 9.3    | 24     | 3.3      | 13.8   | NA                | NA                | NA           | 12.6        | 7.4           | 55.3             | NA                    | NA     | 88      | NA          |
| Anurag Mehta           | 50.2| 56.5     | 18.3   | 24.2   | 1.1      | 5.9    | NA                | NA                | NA           | 9.1         | 82.3          | 26.9             | 6.5                   | NA     | NA      | NA          |
| Olivia D Lara          | 64  | NA       | 31     | 57     | 3        | 7      | 23                | 7                 | 26           | NA          | 0             | 100              | 57                    | 13.6   | 30.3    | 54.5        |
| Javier Garde-Noguera   | 63  | 57.8     | NA     | NA     | NA       | NA     | NA                | NA                | NA           | 29.5        | NA             | 89.5             | NA                    | NA     | 6.2      | NA          |
| Carlo Aschele          | 65  | 43.1     | NA     | NA     | NA       | NA     | NA                | NA                | NA           | 9.1         | NA             | NA               | NA                    | NA     | NA      | NA          |
| Alexia Francesa Bertuzzi| 69.5| NA       | NA     | NA     | NA       | NA     | NA                | NA                | NA           | NA          | NA             | NA               | NA                    | 82     | NA      | 82.3        |
| Antonio Calles         | 68.1| 56.6     | NA     | NA     | NA       | NA     | NA                | 28.5              | NA           | NA          | 100           | 78.1             | NA                    | NA     | NA      | NA          |
| Nathanael R Fillmore   | NA  | NA       | NA     | NA     | NA       | NA     | NA                | NA                | NA           | NA          | NA             | NA               | NA                    | NA     | NA      | NA          |
| Astrid Liévre          | NA  | 26       | 5      | 16     | 3        | NA     | 54                | NA                | 3            | 2           | 5              | 40               | NA                    | 29     | NA      | NA          |

Note: Values are given as means unless otherwise specified.
Abbreviations: DM, diabetes mellitus; HP, hypertension; COPD, chronic obstructive pulmonary disease; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MV, mechanical ventilation; ICU, intensive care unit; NA, not available.
PubMed was performed as follow: ((immune) OR (immunotherapy) OR (checkpoint) OR (immune checkpoint) OR (immune checkpoint inhibitor)) AND ((cancer OR neoplasm OR malignancy)) AND ((COVID-19) OR (SARS-CoV-2)). Various combinations of key words and different search strategies were developed for other databases. All eligible studies met the following conditions: (1) study design: English-published retrospective or prospective studies; (2) study population: cancer patients (solid cancers or hematological malignancies); (3) intervention: ICI treatment; (4) comparison: other anti-tumor treatments; (5) outcome measure: the incidence and mortality of COVID-19. Exclusion criteria were as follows: Case reports, studies without incidence and mortality, review articles, conference abstracts, comments, animal and in vitro experiments, and duplicate reports.

2.2. Literature review and data extraction

The literature review and data extraction were completed by 2 investigators (SHL and YLL) independently. In case of duplicate records pertaining to a single study, we considered the PubMed database to take precedence. Disagreements were handled by discussion for consensus. Quality assessment was completed using the Newcastle Ottawa quality assessment scale (NOS scale). Data extraction included patient characteristics [age, gender, smoke history, hypertension proportion, diabetes proportion, chronic obstructive pulmonary disease (COPD) proportion, heart failure proportion, kidney disease proportion, angiotensin-converting enzyme inhibitors / angiotensin receptor blockers (ACEI/ARB) use proportion, hormone use proportion, lung cancer proportion, solid tumor proportion, metastatic tumor proportion, mechanical ventilation (MV) use proportion, intensive care unit (ICU) stay proportion, hospital admission proportion].

2.3. Postoperative outcomes

The primary endpoint was incidence of COVID-19. The secondary endpoints were mortality of COVID-19.

2.4. Statistical analyses

According to Cochrane Handbook for Systematic Reviews of Interventions on studies, the odds ratio (OR) with 95% confidence interval (CI) was calculated for dichotomous outcomes (reported with incidence). Heterogeneity was assessed with the inconsistency statistic ($I^2$). Random-effects models were used to analyze the data regardless of the heterogeneity in results and study clinical characteristics. Publication bias was assessed by Begg’s test, Egger’s test. Meta-regression and subgroup analysis were conducted to explore the potential sources of significant heterogeneity. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates. $P < 0.05$ (2 sided) was considered to be statistically significant. All statistical analyses were performed in REVMAN (version 5.0; Cochrane Collaboration, Oxford, UK) and Stata (version 16; StataCorp LP).

3. Results

3.1. Study characteristics

Fig. 1 shows the PRISMA flow chart for the study screening and selection process in this research. Twenty-three trials including 19 retrospective studies[21,23,25–41] and 4 prospective studies[22,42–44], enrolling 117,735 study subjects ultimately met our criteria (Fig. 1). Six studies were performed in USA[25,26,29,31,35,40], five in Italy[27,28,38,39,42], four in Spain[27,36,37,43], three in United Kingdom[22,33,34], two in China[23,30], one in France[41], one in India[32] and one in Australia[21]. All articles are of high quality because of NOS score $\geq$5 (Table 3 and Table 4).
| Study                        | Selection | Comparability | Outcome | Total score |
|-----------------------------|-----------|---------------|---------|-------------|
|                            | Representativeness of the exposed cohort | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts |
| Lennard YW                  | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Mario                       | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Mandala                     | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Marina Chiara Garassino     | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Maria Antonietta Igró       | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Aljosja Rogiers             | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Jia Luo                     | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Maria Gonzalez-Cao          | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Mengyuan Dai                | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Vikas Mehta                 | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Kunyu Yang                  | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| David J. Pinato             | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Valerie E. Crolley          | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Anurag Mehta                | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Olivia D Lara               | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Javier Garde-Nogueria       | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Carlo Aschele               | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Antonio Calles              | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Nathanael R Fillmore        | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Astrid Lüevre               | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
| Ramón Yorza                 | ★ ★ ★ ★ ★ | ★ ★ ★ | ★ | ★ | ★ ★ ★ ★ ★ ★ ★ |
For the main outcomes, eleven studies included the incidence of COVID-19 owing to the ICIs treatment, and nineteen for the mortality. Detailed study design and patient characteristics (including the anti-tumor treatment characteristics and the diagnostic method of COVID-19) were reported in Table 1 and 2.

### 3.2. Effect of prior exposure to ICIs treatment on incidence of COVID-19 among cancer patients

Eleven studies provided the data assessed the relationship between ICIs treatment and the incidence of COVID-19 in cancer patients. The result showed the incidence of COVID-19 infection was not significantly increased in cancer patients who were previously treated with ICIs (OR, 0.84; 95 %CI, 0.60–1.18; P = 0.32;  I² = 63.63%; Fig. 2). There was no evidence of significant publication bias (Begg’s test, P = 1.24; Egger’s test, P = 0.93). To evaluate this relationship in greater detail, we analyzed the incidence of COVID-19 compared ICIs with other anti-cancer treatments including chemotherapy, targeted therapy. Prior exposure to ICIs did not significantly reduce the incidence of COVID-19 infection in cancer patients compared with chemotherapy (7 studies; OR, 0.72; 95 %CI, 0.40–1.28; P = 0.26; I² = 76.9%; Fig. 3). No significant difference between prior exposure to ICIs and the targeted therapy existed in this meta-analyses. (7 studies; OR, 1.09; 95% CI, 0.55–2.13; P = 0.81; I² = 71.5%; Fig. 4). We were unable to extend our analysis to patients on other treatments such as hormone therapy, surgery, radiotherapy and other treatment due to the scant data.

Subgroup analyses for the potential sources of significant heterogeneity were listed in Table 5. According to different characteristics, we divided study participants into five groups such as age (≥67 versus < 67 years), male proportion (≥57% versus < 57%), lung cancer proportion (≥30% versus < 30%), solid tumor proportion (≥90% versus < 90%), metastatic tumor proportion (≥80% versus < 80%). There was
significant difference in COVID-19 incidence between subgroup metastatic tumor proportion (P = 0.008), and ICIs significantly reduced the risk of COVID-19 in subgroup metastatic tumor proportion ≥80% compared with other treatments (OR, 0.56; 95% CI, 0.36–0.90; P = 0.03; $I^2 = 0\%$). No significant differences for the incidence of COVID-19 in other subgroups existed.

Meta-regression analyses performed for the potential sources of significant heterogeneity were listed in Table 6, and there were no significant differences for the incidence of COVID-19 in all the subgroups except the group of metastatic tumor proportion ≥80% (P = 0.006).

Sensitivity analyses excluding each included study at a time revealed that all the studies were consistent with the direction and size of the COVID-19 infection incidence of ICIs (P for all < 0.05).

### Table 5
Subgroup analyses using Random effect model for the effect of baseline characteristics (possible confounders) on the association between prior exposure to ICIs and incidence of COVID-19 infection in cancer patients.

| Subgroup          | Endpoint | No. of Comparisons | OR  | 95% CI        | P Value | $I^2$  | P_{difference} Value |
|-------------------|----------|---------------------|-----|---------------|---------|-------|---------------------|
| 1. Age(years)     | Incidence| 9                   | 0.99| 0.71 – 1.38   | 0.23    | 51.6% | 0.231               |
| ≥67               |          |                     | 1.34| 0.76 – 2.36   | 0.321   | 14.3% |                     |
| <67               |          |                     | 0.87| 0.57 – 1.32   | 0.42    | 65.4% |                     |
| 2. Gender(Male%)  | Incidence| 9                   | 0.92| 0.66 – 1.32   | 0.17    | 56.6% | 0.812               |
| ≥57               |          |                     | 0.96| 0.58 – 1.61   | 0.45    | 61.2% |                     |
| <57               |          |                     | 0.88| 0.54 – 1.45   | 0.51    | 57.2% |                     |
| 3. Lung cancer (%)| Incidence| 5                   | 1.06| 0.63 – 1.81   | 0.055   | 56.9% | 0.114               |
| ≥30               |          |                     | 1.84| 0.69 – 4.94   | 0.119   | 58.8% |                     |
| <30               |          |                     | 0.78| 0.52 – 1.17   | 0.342   | 6.9%  |                     |
| 4. Solid tumor (%)| Incidence| 6                   | 0.89| 0.46 – 1.73   | 0.11    | 75.2% | 0.615               |
| ≥90               |          |                     | 1.12| 0.35 – 3.52   | 0.41    | 88.4% |                     |
| <90               |          |                     | 0.79| 0.39 – 1.60   | 0.253   | 27.3% |                     |
| 5. Metastatic tumor (%) | Incidence| 6                  | 0.98| 0.60 – 1.61   | 0.235   | 59.7% | 0.008               |
| ≥80               |          |                     | 0.56| 0.36 – 0.90   | 0.03    | 0%    |                     |
| <80               |          |                     | 1.40| 0.86 – 2.28   | 0.506   | 30.9% |                     |

Abbreviations: OR, Odds ratio; CI, confidence interval.
P Value means the test for the overall effect in each group.
$P_{\text{difference}}$ Value means the test for the subgroup difference.

### 3.3. Effect of prior exposure to ICIs treatment on mortality of COVID-19 among cancer patients

The mortality was reported in nineteen studies. There was no statistically significant reduction in mortality owing to prior exposure to ICIs treatment (19 studies; OR, 1.22; 95% CI, 0.91–1.62; P = 0.18; $I^2 = 25.9\%$; Fig. 5). There was no evidence of significant publication bias (Begg’s test, P = 1.42; Egger’s test, P = 0.60). For further research, there was no significant difference between prior exposure to ICIs and chemotherapy for the mortality of COVID-19 in cancer patients (14
studies; OR, 1.01; 95 %CI, 0.76–1.34; P = 0.97, I² = 0%; Fig. 6). The same results occurred between prior exposure to ICIs and targeted therapy (11 studies; OR, 1.44; 95 %CI, 0.99–2.08; P = 0.055, I² = 0%; Fig. 7).

In the result of subgroup analysis presented in Table 7, we further observed that no statistically significant tests of interaction existed according to different characteristics such as age (≥68 versus <68 years), male proportion (≥56.7% versus <56.7%), smoke history (≥35% versus <35%), hypertension proportion (≥45% versus <45%), diabetes proportion (≥17% versus <17%), COPD proportion (≥12% versus <12%), heart failure proportion (≥14% versus <14%), kidney disease proportion (≥7% versus <7%), ACEI/ARB use proportion (≥20% versus <20%), hormone use proportion (≥10% versus <10%), lung cancer proportion (≥20% versus <20%), solid tumor proportion (≥85% versus <85%), metastatic tumor proportion (≥50% versus <50%), MV use proportion (≥10% versus <10%), ICU stay proportion (≥15% versus <15%), hospital admission proportion (≥70% versus <70%).

Meta-regression analyses performed for the potential sources of significant heterogeneity were listed in Table 8, and there were no significant differences for the mortality of COVID-19 in all the subgroups. Sensitivity analyses excluding each included study at a time revealed that all the studies were consistent with the direction and size of the mortality of ICIs (P for all < 0.05).

4. Discussion

In this meta-analyses of twenty-three trails involving 117,735 cancer patients, we found that there was no statistically significant association between prior exposure to ICIs treatment and the incidence and mortality of COVID-19 infection in cancer patients. Subgroup analyses and meta-analyses indicated that ICIs treatment reduced the incidence of COVID-19 in patients with metastatic cancer.

Cancer patients have been deemed as a susceptible population for COVID-19 with an approximately 2-fold higher risk than non-cancer patients [3,23,45]. Moreover, cancer directed treatment have to been reassessed the balance between the risks and benefits, within the context of the increased risk of infection and mortality by COVID-19 [46–48]. ICIs included anti-CTLA-4 and anti-PD-1/-PD-L1 antibodies are currently the standard scheme in several types of advanced or metastatic

| Study               | OR with 95% CI | Weight (%) |
|---------------------|---------------|------------|
| Ramón Yarza         | 0.15 [0.01, 1.83] | 1.21 |
| Astrid Liévre       | 1.82 [1.12, 2.95] | 14.20 |
| Antonio Calles      | 2.21 [0.36, 13.69] | 2.27 |
| Justin Lee          | 1.70 [0.89, 3.24] | 10.83 |
| Alexia Francesca Bertuzzi | 0.35 [0.01, 10.25] | 0.71 |
| Olivía D Lara       | 3.49 [1.08, 11.27] | 4.81 |
| Anurag Mehta        | 0.40 [0.04, 3.77] | 1.54 |
| David J. Pinato     | 0.80 [0.46, 1.40] | 12.56 |
| Kanyu Yang          | 1.17 [0.15, 9.02] | 1.83 |
| Vikas Mehta         | 0.95 [0.10, 9.00] | 1.53 |
| Mengyuan Dai        | 9.07 [1.59, 51.70] | 2.45 |
| Maria Gonzalez-Cao  | 0.84 [0.23, 3.06] | 4.09 |
| Jia Luo             | 1.13 [0.25, 5.07] | 3.19 |
| Aljosja Rogiers     | 0.62 [0.22, 1.76] | 5.77 |
| Marina Chiara Garassino | 0.89 [0.40, 1.99] | 8.34 |
| Nathanael R Fillmore | 0.80 [0.17, 3.80] | 2.98 |
| Nikolai Klebanov    | 1.60 [0.78, 3.29] | 9.55 |
| Mario Mandala       | 2.28 [0.43, 12.04] | 2.66 |
| Lennard YW Lee      | 0.74 [0.36, 1.53] | 9.49 |
| **Overall**         | 1.22 [0.91, 1.62] | |

Random-effects DerSimonian-Laird model
It remains unclear about the immune effect and the real impact of COVID-19 infection by ICIs. The incidence of COVID-19 and clinical outcome of cancer patients with COVID-19 infection prior exposure to ICIs are controversial. The study conducted by Maria Antonietta Isgrò have showed that ICIs could protect cancer patients from COVID-19 infection [28]. However, another real-world study performed by Alexia Francesca Bertuzzi did not show a high risk for COVID-19 infection in cancer patients treated with ICIs [39]. According to Luo J [29] and Marina Chiara Garassino’s [27] studies, ICIs did not increase the mortality for thoracic cancer patients with COVID-19. However, two previous Chinese studies reported an increased risk of death with recent immunotherapy [23, 52]. Previously, a few meta-analyses and reviews, aiming to evaluate the effect of ICIs on cancer patients during the COVID-19 pandemic, were published, and both of the results were
Table 7
Subgroup analyses using Random effect model for the effect of baseline characteristics (possible confounders) on the association between prior exposure to ICIs and mortality of COVID-19 infection in cancer patients.

| Subgroup               | Endpoint   | No. of Comparisons | OR       | 95% CI          | P Value | I² | PDifference Value |
|------------------------|------------|---------------------|----------|-----------------|---------|----|-------------------|
| 1. Age(years)          | Mortality  | 15                  | 1.11     | 0.80 ~ 1.54     | 0.26    | 17.3% | 0.076             |
| ≥68                    | 8          | 0.85                | 0.60 ~ 1.20 | 0.976          | 0%      |     |                   |
| <68                    | 7          | 1.68                | 0.86 ~ 3.29 | 0.108          | 42.4%   |     |                   |
| 2. Gender(Male%)       | Mortality  | 16                  | 1.18     | 0.88 ~ 1.66     | 0.166   | 26.5% | 0.942             |
| ≥56.7                  | 8          | 1.19                | 0.85 ~ 1.48 | 0.262          | 21.1%   |     |                   |
| <56.7                  | 8          | 1.16                | 0.61 ~ 2.18 | 0.117          | 39.4%   |     |                   |
| 3. Previous DM (%)     | Mortality  | 14                  | 1.20     | 0.83 ~ 1.73     | 0.059   | 40.2% | 0.479             |
| ≥17                    | 7          | 1.38                | 0.85 ~ 2.24 | 0.171          | 33.6%   |     |                   |
| <17                    | 7          | 1.05                | 0.59 ~ 1.87 | 0.075          | 47.7%   |     |                   |
| 4. Smoke history (%)   | Mortality  | 8                   | 1.65     | 1.02 ~ 2.68     | 0.10    | 41.7% | 0.201             |
| ≥35                    | 4          | 1.35                | 0.79 ~ 2.29 | 0.138          | 45.6%   |     |                   |
| <35                    | 4          | 2.72                | 1.07 ~ 6.91 | 0.219          | 32.3%   |     |                   |
| 5. HP (%)              | Mortality  | 12                  | 1.23     | 0.83 ~ 1.84     | 0.051   | 43.8% | 0.176             |
| ≥45                    | 6          | 1.59                | 1.14 ~ 2.22 | 0.488          | 0%      |     |                   |
| <45                    | 6          | 0.92                | 0.45 ~ 1.89 | 0.088          | 47.9%   |     |                   |
| 6. COPD proportion (%) | Mortality  | 12                  | 1.20     | 0.84 ~ 1.71     | 0.213   | 23.5% | 0.902             |
| ≥12%                   | 6          | 1.12                | 0.73 ~ 1.73 | 0.667          | 0%      |     |                   |
| <12%                   | 6          | 1.18                | 0.59 ~ 2.36 | 0.060          | 52.9%   |     |                   |
| 7. HF proportion (%)   | Mortality  | 12                  | 1.30     | 0.88 ~ 1.91     | 0.071   | 40.5% | 0.151             |
| ≥14%                   | 6          | 1.04                | 0.58 ~ 1.89 | 0.113          | 43.9%   |     |                   |
| <14%                   | 6          | 1.73                | 1.21 ~ 2.47 | 0.616          | 0%      |     |                   |
| 8. KD proportion (%)   | Mortality  | 9                   | 1.40     | 0.79 ~ 2.50     | 0.086   | 42.2% | 0.703             |
| ≥7%                    | 5          | 1.50                | 0.94 ~ 2.38 | 0.399          | 1.3%    |     |                   |
| <7%                    | 4          | 1.10                | 0.24 ~ 5.07 | 0.076          | 67.1%   |     |                   |
| 9. ACEI/ARB (%)        | Mortality  | 4                   | 1.40     | 0.66 ~ 2.99     | 0.063   | 59%  | 0.554             |
| ≥20%                   | 2          | 1.64                | 0.43 ~ 6.23 | 0.059          | 71.9%   |     |                   |
| <20%                   | 2          | 0.73                | 0.07 ~ 7.68 | 0.060          | 71.8%   |     |                   |
| 10. Hormone (%)        | Mortality  | 5                   | 1.16     | 0.72 ~ 1.89     | 0.061   | 55.6% | 0.515             |
| ≥10%                   | 2          | 1.37                | 0.69 ~ 2.72 | 0.134          | 55.4%   |     |                   |
| <10%                   | 3          | 0.96                | 0.42 ~ 2.18 | 0.071          | 62%     |     |                   |
| 11. Lung cancer (%)    | Mortality  | 11                  | 1.24     | 0.81 ~ 1.90     | 0.065   | 41.2% | 0.245             |
| ≥20%                   | 6          | 1.63                | 0.81 ~ 3.26 | 0.119          | 48.7%   |     |                   |
| <20%                   | 5          | 0.99                | 0.61 ~ 1.60 | 0.342          | 6.9%    |     |                   |
| 12. Solid tumor (%)    | Mortality  | 7                   | 1.01     | 0.69 ~ 1.48     | 0.704   | 0%   | 0.110             |
| ≥85%                   | 4          | 1.46                | 0.81 ~ 2.63 | 0.830          | 0%      |     |                   |
| <85%                   | 3          | 0.78                | 0.47 ~ 1.28 | 0.835          | 0%      |     |                   |
| 13. MT proportion (%)  | Mortality  | 13                  | 1.30     | 0.87 ~ 1.94     | 0.45    | 43.9% | 0.210             |
| ≥50%                   | 6          | 1.67                | 1.14 ~ 2.43 | 0.410          | 1.0%    |     |                   |
| <50%                   | 7          | 1.05                | 0.57 ~ 1.94 | 0.046          | 53.1%   |     |                   |
| 14. MV proportion (%)  | Mortality  | 10                  | 1.13     | 0.79 ~ 1.61     | 0.251   | 20.9% | 0.788             |
| ≥10%                   | 5          | 1.18                | 0.65 ~ 2.15 | 0.290          | 19.6%   |     |                   |
| <10%                   | 5          | 1.06                | 0.63 ~ 1.78 | 0.192          | 34.4%   |     |                   |
| 15. ICU (%)            | Mortality  | 9                   | 1.17     | 0.80 ~ 1.70     | 0.255   | 21.1% | 0.771             |
| ≥15%                   | 4          | 1.30                | 0.55 ~ 3.04 | 0.195          | 36.2%   |     |                   |
| <15%                   | 5          | 1.13                | 0.73 ~ 1.75 | 0.246          | 26.3%   |     |                   |
| 16. hospital (%)       | Mortality  | 9                   | 1.17     | 0.80 ~ 1.73     | 0.173   | 30.6% | 0.056             |
| ≥70%                   | 4          | 0.82                | 0.53 ~ 1.25 | 0.961          | 0%      |     |                   |
| <70%                   | 5          | 1.59                | 0.93 ~ 2.72 | 0.240          | 27.3%   |     |                   |

Abbreviations: OR, Odds ratio; CI, confidence interval; DM, diabetes mellitus; HP, hypertension; COPD, chronic obstructive pulmonary disease; HF, heart failure; KD, kidney disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MT, metastatic tumor; MV, mechanical ventilation; ICU, intensive care unit.

Abbreviations: OR, Odds ratio; CI, confidence interval.

P Value means the test for the overall effect in each group.
PDifference Value means the test for the subgroup difference.

negative[53,54]. Compared with the latest meta-analyses performed by Gilbert Lazarus[53] from eight studies which focused on the mortality, our analyses included eleven more studies showed the same result for the mortality and provided available evidence from eleven studies about the incidence of COVID-19 by ICIs.

Compared with chemotherapy which leads to immunodeficiency, ICIs can activate the immune system against cancer, but they could also trigger inflammatory storm of the activated immune system and damage.
considering that some findings were associated with high heterogeneity, the random effect model was used for our meta-regression analyses. Moreover, we conducted the sensitivity analyses, subgroup analyses and meta-regression to minimize the impact of heterogeneity, and found that the results did not change. Thirdly, the main outcome of included studies was different, and this led to heterogeneity between the outcomes. Some outcome (COVID-19 severity, hospitalization, and ICU admission) which included in other meta-analyses was not reported in our study, because of no enough data and low evidence quality. Fourthly, which kind of ICIs was not clarified in most of the included studies, and further studies are required to confirm the definite drug of ICIs for incidence and mortality of COVID-19. Fifthly, we did not compare ICIs with other treatments such as surgery and radiotherapy, not only owing to the lack of data, but also usually surgery for patients with early stage of cancer and radiotherapy for local region treatment. Last, many design differences among these studies made it difficult to reduce clinical heterogeneity. We were unable to performed the subgroup analyses and meta-regression based on individual information of the included patients owing to no available and detailed data.

5. Conclusions

In summary, available evidence from our meta-analyses suggests that prior exposure to ICIs was not associated with an increased risk of COVID-19 incidence and mortality in cancer patients. Subgroup analyses and meta-analyses indicated that ICIs may reduce the infection susceptibility of COVID-19 in metastatic cancer patients. Further studies with large and well-designed prospective trails are required to explore the association between prior exposure to ICIs with incidence and outcome of COVID-19 in patients with cancer.

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CRediT authorship contribution statement

Yang Liu: Conceptualization, Formal analysis, Methodology, Software. Shuo Liu: Data curation. Yujun Qin: Formal analysis, Methodology, Software. Lei Zhao: Formal analysis, Methodology, Software. Yiliang Li: Data curation, Funding acquisition, Resources, Investigation, Project administration, Validation. Chenghui Zhou: Investigation, Project administration, Validation, Writing – review & editing. Wei Chen: Conceptualization, Investigation, Project administration, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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