Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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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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ABSTRACT

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.

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.

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 infectioin. Our subgroup and *meta*-regression analyses indicated that prior exposure to ICIs may reduce the incidence of COVID-19 in metastatic cancer patients.

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. 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 cell 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

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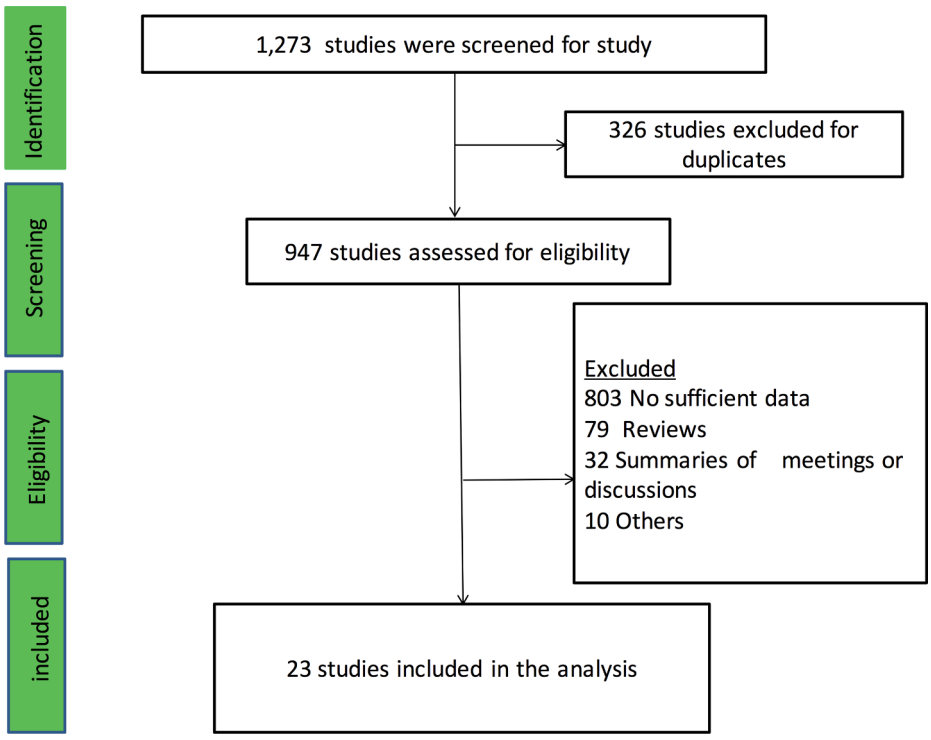

Fig. 1. Flow diagram of studies included into *meta*-analyses

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, hormonetherapy, 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
Aljosja 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	within 40 days before the onset of COVID-19 symptoms	Mortality

(*continued on next page*)

Table 1 (*continued*)

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
Vikas Mehta	USA	Retrospective, Single center	March 18, 2020 to April 8, 2020	Chemotherapy, radiotherapy	218	RT-PCR	30 days prior to COVID-19 diagnosis	Mortality
Kunyu Yang	China	Retrospective, Multi center	Jan 13, 2020 to Mar 18, 2020	Chemotherapy, radiotherapy, targeted treatment	205	RT-PCR and next-generation sequencing analysis	4 weeks before the onset of COVID-19 symptoms	Mortality
David J. Pinato	UK	Retrospective, Multi center	February 26,2020 to April 1, 2020	Chemotherapy, hormonetherapy, targeted treatment	890	A nasopharyngeal swab and RT-PCR assay	within 4 weeks of COVID-19 diagnosis	Incidence and mortality
Valerie E. Crolley	UK	Retrospective, Multi center	March 2,2020 to May 31, 2020	Chemotherapy, hormonetherapy, targeted treatment	2791	RT-PCR	NA	Incidence
Anurag Mehta	India	Retrospective, Single center	June 8,2020 to August 20, 2020	Chemotherapy, radiotherapy,surgery, targeted treatment	3101	RT-PCR assay or cartridge-based nucleic acid	within a month of COVID-19 diagnosis	Mortality
Olivia D Lara	USA	Retrospective, Multi center	March 1, 2020, and April 22, 2020	Chemotherapy, hormonetherapy, radiotherapy,surgery, targeted treatment	121	RT-PCR or positive serology test or radiologic imaging	within 30 and 60 days of the COVID-19 diagnosis	Mortality
Javier Garde-Noguera	Spain	Retrospective, Single center	February 28, 2020 to April 30,2020	Chemotherapy, targeted treatment	215	A nasopharyngeal swab and RT-PCR assay	within 2 month of COVID-19 diagnosis	Incidence
Carlo Aschele	Italy	Retrospective, Multi center	January 15, 2020, to May 4, 2020,	Chemotherapy, targeted treatment, other treatment	59 989	A nasopharyngeal swab and RT-PCR assay	at least 1 course prior to COVID-19 diagnosis	Incidence
Alexia Francesca Bertuzzi	Italy	Retrospective, Single center	February 21,2020 to April 30,2020	Chemotherapy, targeted treatment, other treatment	1267	nasopharyngeal swab or bronchoalveolar lavage and RT-PCR assay	NA	Incidence and mortality
Antonio Calles	Spain	Retrospective, Single center	March 4, 2020 and May 12, 2020	Chemotherapy, targeted treatment	23	RT-PCR	<30 days or < 2 weeks from last dose of systemic therapy	Incidence and mortality
Nathanael R Fillmore	USA	Retrospective	January 1, 2020, and May 4, 2020	Chemotherapy, hormonetherapy, targeted treatment	22,914	NA	6 months prior to COVID-19 diagnosis	Incidence and mortality
Astrid Lièvre	France	Retrospective, Multi center	April 4 ,2020 to June 11, 2020	Chemotherapy, hormonetherapy, targeted treatment	1289	RT-PCR or radiologic imaging	within 1 month or 3 month of COVID-19 diagnosis	Mortality
Ramón Yarza	Spain	Prospective, Single center	March 9, 2020 to April 19,2020	Chemotherapy, hormonetherapy, targeted treatment	63	RT-PCR or positive serology test	1 month prior to COVID-19 diagnosis	Mortality

Abbreviations: COVID-19, coronavirus disease 2019; USA, the United States of America; UK, United Kingdom; ICI,immune checkpoint inhibitor; RT-PCR, reverse transcription-polymerase chain reaction; IQR, interquartile range; NA, not available.

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 has 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 mortality 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

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	NA	3.7	9	NA	21.3	NA	NA	NA
Lennard YW Lee	69	56	16	31	8	14	NA	NA	NA	NA	11	NA	43	NA	7	NA
MarioMandala	66.5	67.3	25	NA	27.3	80.7	NA	8	NA	NA	33.3	NA	74.8	72.55	NA	3.4
NikolaiKlebanov	66.6	58.1	16.4	53.2	24.1	10.7	NA	15.6	NA	NA	NA	96.1	NA	NA	NA	NA
MarinaChiara Garassino	68	70	15	47	26	15	81	8	28	22	91	NA	74	6	9	76
Maria Antonietta Isgrò	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	5	NA	NA	16	NA	NA	3	32	60
Jia Luo	69	48	30	55	17	7	NA	NA	NA	NA	NA	NA	NA	20	23	63
Maria Gonzalez-Cao	68	59	NA	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	6	70
Mengyuan Dai	64	54.7	6.7	28.6	8.6	16.2	34.3	5.7	NA	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	24.8	NA	NA	NA	NA	19.3	20.6	10.6	NA
Kunyu 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	NA	4.7	NA	84.6	43.8	10.9	NA	85.4
Valerie E. Crolley	64	48.1	9.3	24	3.3	13.8	NA	NA	NA	12.6	7.4	55.3	NA	NA	NA	88
Anurag Mehta	50.2	56.5	18.3	24.2	1.1	5.9	NA	NA	NA	NA	9.1	82.3	26.9	6.5	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	NA	29.5	NA	89.5	NA	NA	6.2
Carlo Aschele	65	43.1	NA	NA	NA	NA	NA	NA	NA	NA	9.1	NA	NA	NA	NA	NA
Alexia Francesca Bertuzzi	69.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	82	NA	NA	82.3
Antonio Calles	68.1	56.6	NA	NA	NA	NA	28.5	NA	NA	NA	100	100	78.1	NA	NA	NA
Nathanael R Fillmore	NA	NA	NA	NA	NA	NA	19.8	NA	NA	NA	NA	NA	NA	NA	NA	NA
Astrid Lièvre	NA	62	21	46	12	8	52	NA	19	15	24	NA	59	5	10	65
Ramón Yarza	NA	26	5	16	3	NA	54	3	2	5	40	NA	29	NA	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.

Table 3
Summarized Quality Assessment of Included Case-control studies (Newcastle-Ottawa Quality Assessment Scale criteria).

Study	Selection				Comparability	Exposure		Total score
	Adequate definition of the case	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and control	Non-response rate	
Justin Jee	★		★		★	★	★		★★★★★
Nikolai Klebano	★	★	★	★	★	★	★		★★★★★★
Alexia	★	★	★			★	★		★★★★
Francesca Bertuzzi									

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 no<5 (Table 3 and Table 4).

Table 4
Summarized Quality Assessment of Included Cohort studies (Newcastle-Ottawa Quality Assessment Scale criteria).

Study	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	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 Isgrò	★		★	★	★	★		★	★★★★★★
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-Noguera	★	★	★	★	★	★	★		★★★★★★★
Carlo Aschele	★	★	★	★	★	★	★		★★★★★★★
Antonio Calles	★	★	★	★	★	★	★		★★★★★★★
Nathanael R Fillmore	★	★	★	★	★★	★	★		★★★★★★★★
Astrid Lièvre	★	★	★	★	★★	★	★		★★★★★★★★
Ramón Yarza	★	★	★		★	★	★		★★★★★★

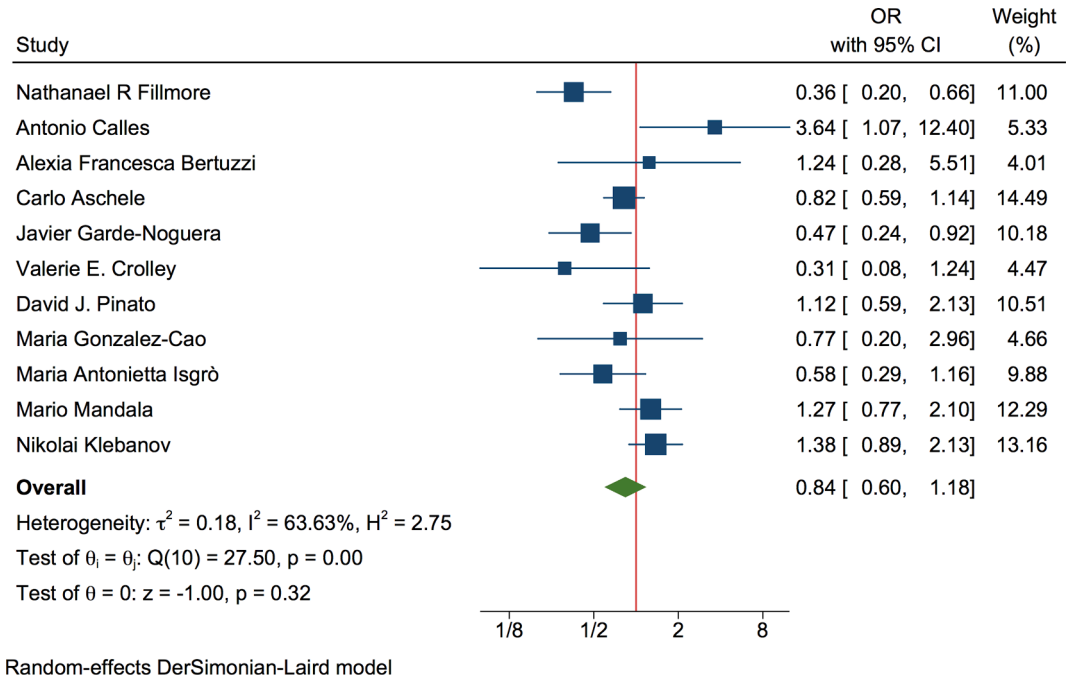

Fig. 2. Forest plot for assessing the incidence of COVID-19 infection in cancer patients previously treated with ICIs versus other anti-cancer treatments

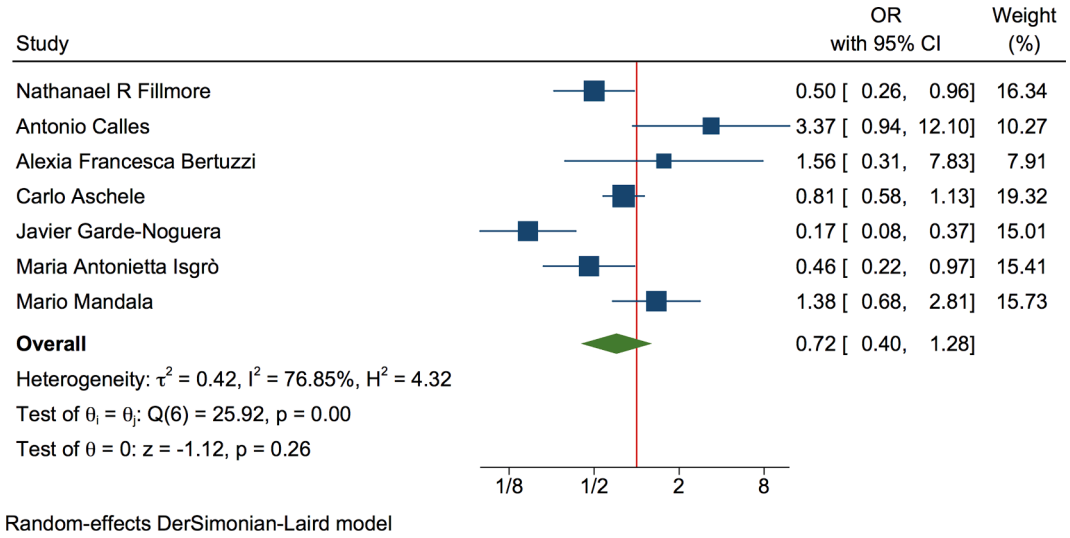

Fig. 3. Forest plot for assessing the incidence of COVID-19 infection in cancer patients previously treated with ICIs versus chemotherapy

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 ICI 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 I^2 = 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, I^2 = 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; I^2 = 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

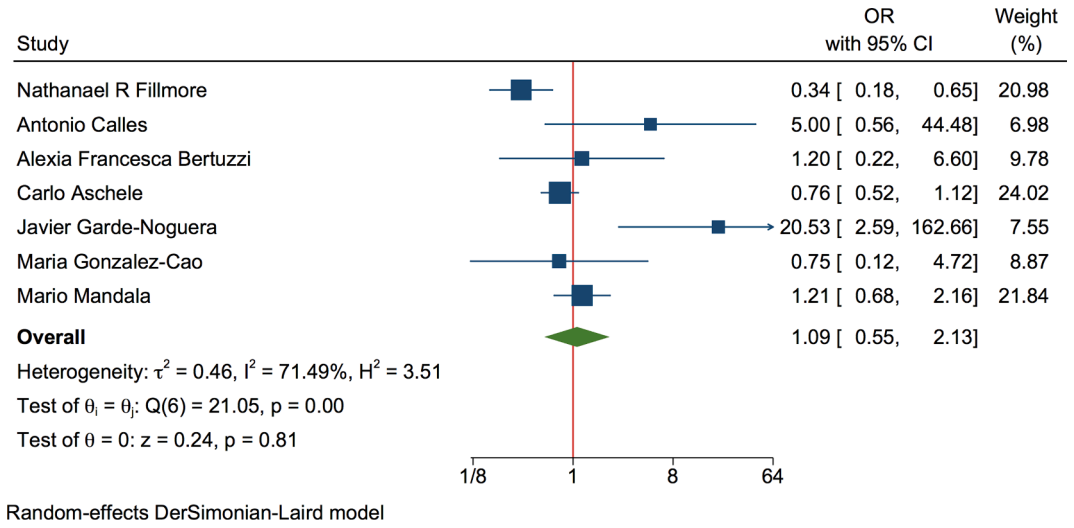

Fig. 4. Forest plot for assessing the incidence of COVID-19 infection in cancer patients previously treated with ICIs versus targeted therapy

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		4	1.34	0.76 ~ 2.36	0.321	14.3%	
<67		5	0.87	0.57 ~ 1.32	0.42	65.4%	
2. Gender(Male%)	Incidence	9	0.92	0.66 ~ 1.29	0.17	56.6%	0.812
≥57		4	0.96	0.58 ~ 1.61	0.45	61.2%	
<57		5	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		2	1.84	0.69 ~ 4.94	0.119	58.8%	
<30		3	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		3	1.12	0.35 ~ 3.52	0.41	88.4%	
<90		3	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		3	0.56	0.36 ~ 0.90	0.03	0%	
<80		3	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.
$P_{Difference}$ Value means the test for the subgroup difference.

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).

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

Table 6
Meta-regression analysis using Random-effects Dersimonian-Laird method 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.

	Regression coefficient	95% CI	P Value
1. Age(years)	0.442	−0.313 ~ 1.197	0.252
2. Gender(Male%)	0.086	−0.629 ~ 0.800	0.814
3. lung cancer (%)	0.837	−0.162 ~ 1.837	0.101
4. solid tumor (%)	0.451	−1.079 ~ 1.981	0.563
5. metastatic tumor (%)	−0.870	−1.492 ~ -0.248	0.006

Abbreviations: COVID-19, coronavirus disease 2019; ICIs, immune checkpoint inhibitors; CI, confidence interval.

studies; OR, 1.01; 95 %CI, 0.76–1.34; P = 0.97, I^2 = 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, I^2 = 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 among 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

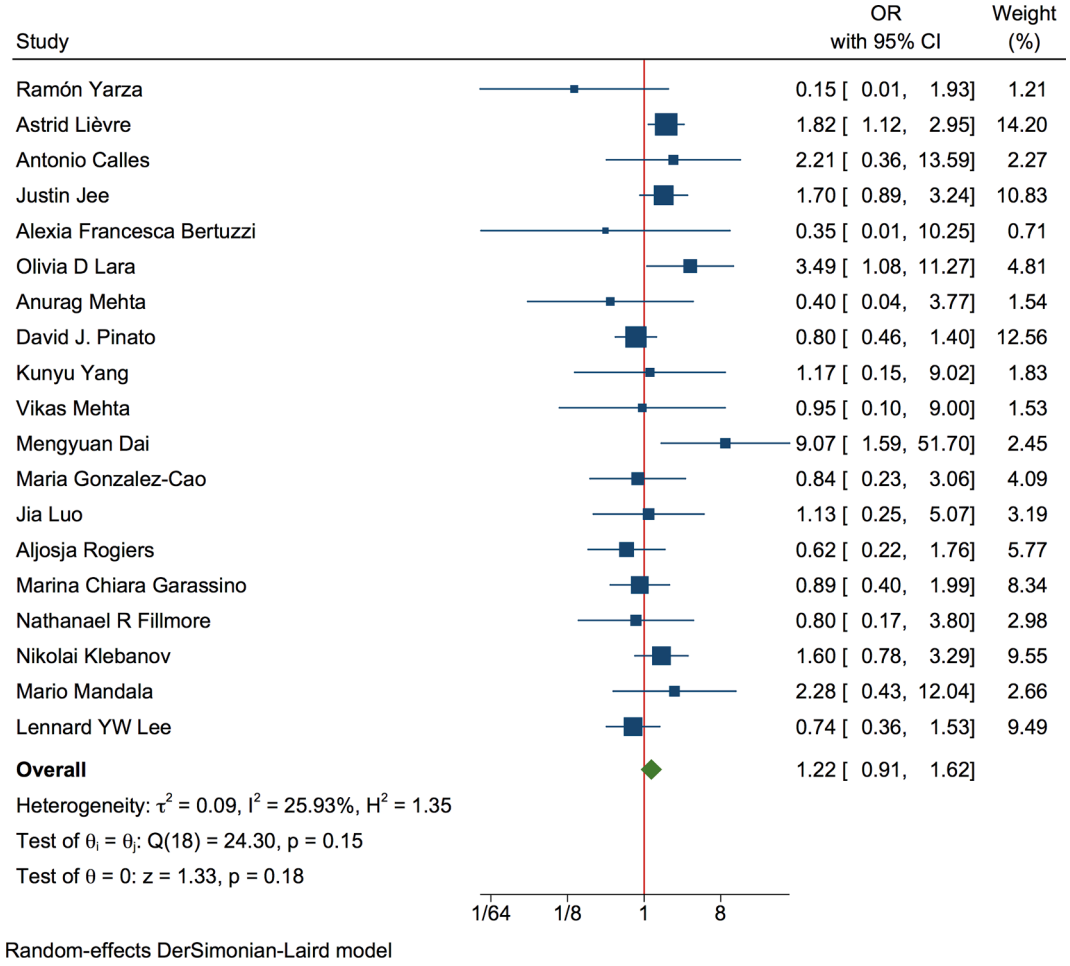

Fig. 5. Forest plot for assessing the mortality of COVID-19 infection in cancer patients previously treated with ICIs versus other anti-cancer treatments

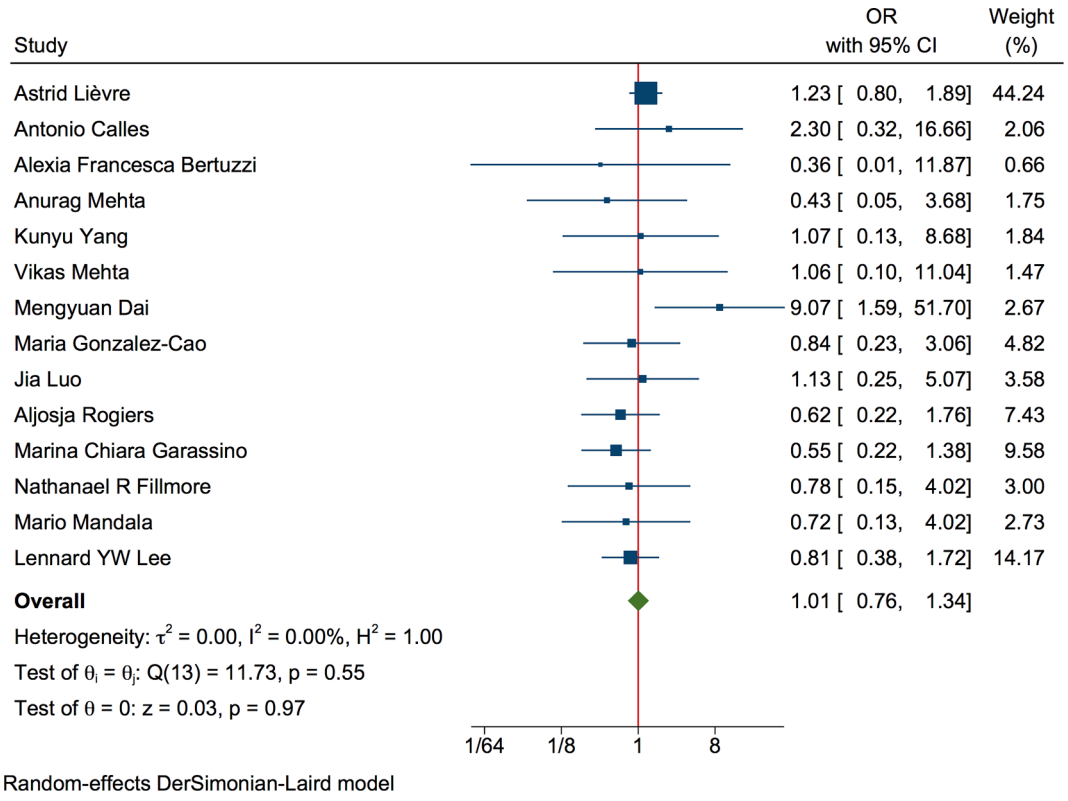

Fig. 6. Forest plot for assessing the mortality of COVID-19 infection in cancer patients previously treated with ICIs versus chemotherapy

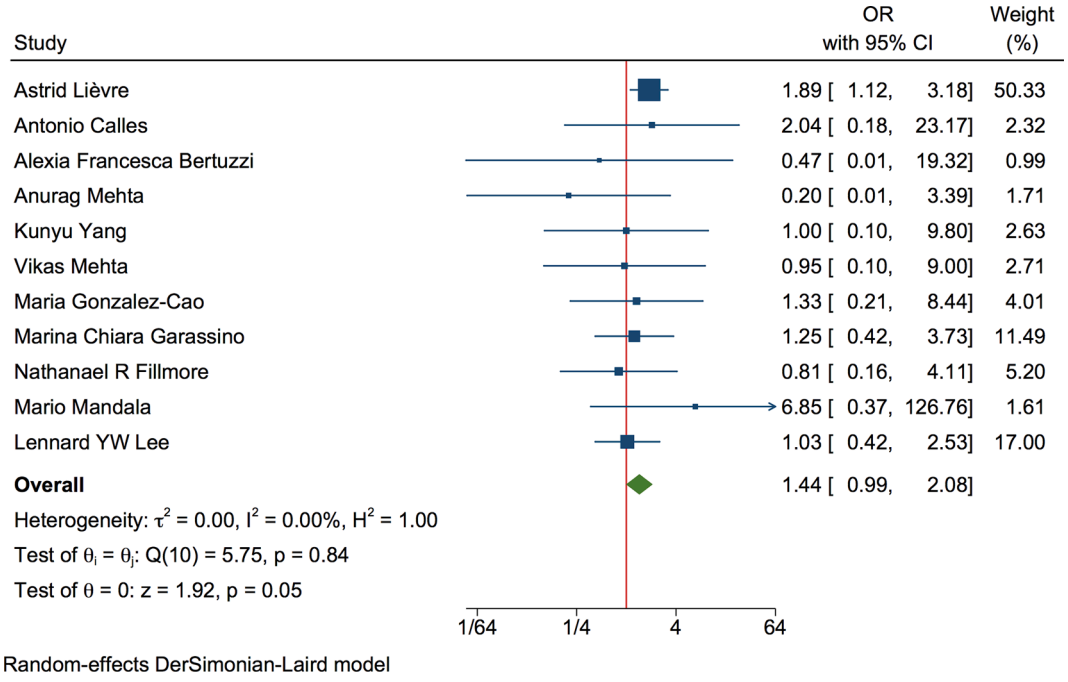

Fig. 7. Forest plot for assessing the mortality of COVID-19 infection in cancer patients previously treated with ICIs versus targeted therapy

tumors[49–51]. 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	I^2	$P_{Difference}$ 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 (%)	Morality	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.
$P_{Difference}$ 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

Table 8
Meta-regression analysis using Random-effects Dersimonian-Laird method 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.

	Regression coefficient	95% CI	P Value
1. Age(years)	−0.646	−1.223 ~ -0.070	0.800
2. Gender(Male%)	0.002	−0.656 ~ 0.659	0.996
3. Previous DM (%)	0.280	−0.477 ~ 1.039	0.468
4.Smoke history (%)	−0.721	−1.747 ~ 0.306	0.169
5.HP proportion (%)	0.561	−0.154 ~ 1.296	0.124
6. COPD proportion (%)	−0.133	−0.886 ~ 0.621	0.730
7. HF proportion (%)	−0.571	−1.224 ~ -0.082	0.086
8. KD proportion (%)	0.368	−0.915 ~ 1.651	0.574
9. ACEI/ARB (%)	0.631	−1.707 ~ 2.969	0.597
10. Hormone (%)	0.316	−0.779 ~ 1.410	0.572
11. Lung cancer (%)	0.540	−0.320 ~ 1.400	0.218
12. Solid tumor (%)	0.629	−0.142 ~ 1.401	0.110
13. MT proportion (%)	0.467	−0.315 ~ 1.249	0.242
14. MV proportion (%)	0.111	−0.688 ~ 0.911	0.785
15. ICU (%)	0.160	−0.732 ~ 1.053	0.725
16.Hospital (%)	−0.703	−1.280 ~ -0.128	0.394

Abbreviations: COVID-19, coronavirus disease 2019; ICIs, immune checkpoint inhibitors; 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.

other organs. The data from the CAPITOL study assessed the relationship between the type of systemic anti-cancer treatment with the risk of contracting COVID-19 and mortality[34]. Oncology patients treated with chemotherapy are significantly more vulnerable to COVID-19, even after adjusted for age, gender and comorbidities (OR 2.99; 95% CI = 1.72–5.21; p = 0.001), and ICIs were not found to be at higher risk of contracting COVID-19 (OR 0.31 95% CI 0.08–1.28; p = 0.11). There was no significant difference in the risk of death in COVID-19 positive patients by treatment received chemotherapy or ICIs. In our studies with larger sample size, prior exposure to ICIs did not reduce the incidence and mortality of COVID-19 infection among cancer patients. Our subgroup and *meta*-regression analyses showed that patients with metastatic tumor may earn a profit from ICIs in the period of COVID-19 pandemic. These provided available evidence to cease chemotherapy in preference of ICIs in metastatic cancer patients with higher risk of COVID-19 infection. The NICE guideline about the delivery of systemic anticancer treatments have advised to increase the usage of targeted therapies, hormonal therapy and immunotherapy and reduce the dose of cytotoxic chemotherapy[55].

Clinical characters such as elderly, male gender, ethnicity, comorbidities (hypertension, ischaemic heart disease, diabetes, chronic lung disease), cancer type (haematological cancer, respiratory and intrathoracic neoplasms), steroid use, treatment intent, the time of anti-tumor treatment before the diagnosis of COVID-19 and anticoagulation appear to be at significantly increased risk for incidence and mortality by COVID-19[30,40]. Our study was corrected by most of the confounding factors and the conclusion did not vary.

Our analyses have several limitations. Firstly, most of included studies are retrospective. Secondly, there is scant data about some confounding factors such as different capability of disease control in different countries, ethnicity, comorbidities (including diabetes, hypertension and obesity), treatment intent, patients with different treatment line and history, the time of anti-tumor treatment before the diagnosis of COVID-19 and anticoagulation, so the result may not show the real effect of ICI treatment on the incidence and mortality of COVID-19. Considering that some findings were associated with high heterogeneity, the random effect model was used for our *meta*-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. Future studies with large and well-designed perspective 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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