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COVID-19 vaccination in patients with cancer receiving immune checkpoint inhibitors: a systematic review and meta-analysis

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ABSTRACT

Background Immune checkpoint inhibitors (ICI) can cause off-target inflammatory and immune-related adverse events (irAE). Conceivably, COVID-19 vaccination could trigger an inflammatory and immune response that could induce or aggravate irAE.

Methods The objective of this systematic review is to appraise the efficacy and safety of COVID-19 vaccination in patients with cancer treated with ICI. The literature search was performed in PubMed and Embase in English from December 2019 to February 2022. The review included clinical trials, observational cohort studies, case series, and case reports reporting on the clinical efficacy and safety of COVID-19 vaccines on patients with cancer treated with ICI. Outcomes of interest included seroconversion, SARS-CoV-2 infection rate, severe COVID-19, COVID-19 mortality rate. Incidence of ICI irAEs was also ascertained as well as vaccine adverse events. A meta-analysis was conducted to estimate the pooled effect sizes of the outcomes when possible, using random effects models.

Results Overall, 19 studies were included for the analysis (n=10 865 with 2477 receiving ICI). We analyzed 15 cohort studies, 1 cross-sectional study, and 3 case reports. There were no statistically significant differences in seroconversion rates after the second dose of the vaccine when comparing patients with cancer receiving ICI with patients without cancer (risk ratio, RR 0.97, 95% CI 0.92 to 1.03) or with patients with cancer without active treatment (RR 1.00, 95% CI 0.96 to 1.04). There was a higher probability of seroconversion in patients with cancer treated with ICI compared with patients with cancer treated with chemotherapy (RR 1.09, 95% CI 1.00 to 1.18). In a single study in patients receiving ICI, no differences were observed in risk of irAE between those receiving inactivated vaccine and those unvaccinated (pneumonitis RR 0.88, 95% CI 0.33 to 2.3; rash RR 1.03, 95% CI 0.66 to 1.62; arthralgia RR 0.94, 95% CI 0.51 to 1.75). There were no studies for other types of vaccines comparing vaccinated vs not vaccinated in patients treated with ICI. The most common vaccine-related adverse events were local pain or fatigue. Overall, the quality of evidence was rated as very low.

Conclusion COVID-19 vaccination appears to be effective and safe in patients with cancer receiving ICI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It has been suggested that COVID-19 vaccines might lead to immune-related adverse event in patients receiving immune checkpoint inhibitor (ICI). Clinical trials that evaluated the efficacy of these vaccines did not include patients with cancer receiving treatment. Several small studies have been published with heterogeneous methods and results.

WHAT THIS STUDY ADDS

⇒ COVID-19 vaccination appears to be safe and effective in patients with cancer receiving ICI, although the quality of the evidence is low.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ COVID-19 vaccination can be recommended for patients with cancer receiving ICI. However, additional well-controlled studies are needed to robustly assess the impact of vaccination in this population with respect to clinical outcomes such as incidence and severity of COVID-19.

BACKGROUND

As we face the third year of the COVID-19 pandemic, vaccination against COVID-19 has exponentially increased, including patient populations with chronic disease. Up to March 2022, 149 COVID-19 vaccines were in clinical development.[1] Available vaccines are highly effective for the prevention of severe COVID-19 and mortality. A recent meta-analysis of 35 randomized control trials showed that the efficacy of vaccines to prevent COVID-19 infection was 95% (95% CI 92% to 97%) for mRNA vaccines, 68% (95% CI 61% to 74%) for viral vector vaccines, and 61% (95% CI 52% to 68%) for inactivated vaccines.[2] None of the trials included pregnant women or immunocompromised participants such as patients with cancer.[3]

Patients with cancer are at high risk of COVID-19 severe complications and death.

Those who are receiving oncological treatment when they acquire COVID-19 have higher risks of death, hospitalization, and intensive care unit (ICU) admission compared with patients with cancer without recent cancer treatment, or patients without cancer.[4] COVID-19 vaccination is highly recommended for patients with cancer, despite a concern about potentially lower efficacy in immunosuppressed patients.[5] Moreover, it has been suggested that COVID-19 vaccination may be a risk factor for immune-related adverse event (irAE) in patients with cancer receiving immune checkpoint inhibitor (ICI).[6–8] Conceivably, both the COVID-19 vaccination and the ICI can independently stimulate the immune system potentiating adverse events.[6] Prior literature on the use of influenza vaccination in patients with cancer receiving ICI, suggests that it is safe.[9]

However, to the best of our knowledge, there are no prior systematic reviews specifically evaluating COVID-19 vaccination in patients with cancer receiving ICI. The aim of this systematic review and meta-analysis is to determine the efficacy and safety of COVID-19 vaccination in this population.

METHODS

This study was registered at PROSPERO (registration number: CRD42022307545; http://www.crd.york.ac.uk/PROSPERO). This study was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses statement.

Eligibility criteria

We included clinical trials, cohort studies (prospective and retrospective), and cross-sectional studies. We also included case series and case reports to identify unusual adverse events potentially associated with vaccination.

We included studies of adults (≥18 years old) with any type of cancer receiving ICI who underwent COVID-19 vaccination. Immune checkpoint inhibitors included: (1) programmed cell death protein 1 (PD-1) inhibitors (pembrolizumab, nivolumab, cemiplimab); programmed death-ligand 1 (PD-L1) inhibitors (atezolizumab, avelumab, durvalumab); and the cytotoxic T lymphocyte-associated protein 4 inhibitor ipilimumab. We considered any comparison group (eg, chemotherapy, no active treatment, healthy individuals). We excluded studies if insufficient information for analysis was provided, studies where the type of immunotherapy received was not specified, and studies on pediatric populations. We included the following 10 COVID-19 vaccines granted emergency use by the WHO: (1) protein subunit vaccines (Novavax (NVX-CoV2373) and COVOVAX of the Serum Institute of India), (2) mRNA vaccines (Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2)), (3) non replicating viral vector vaccines (Janssen (Ad26.COV2.S); Oxford/AstraZeneca (ChAdOx1 nCoV-19); and Covishield of the Serum Institute of India), (4) inactivated vaccines (Bharat Biotech – Covaxin (BBV152)); Sinopharm (BBIBP-CorV); and Sinovac (CoronaVac)). The outcomes of interest were: seroconversion, COVID-19 infection, severe COVID-19, COVID-19 mortality, vaccine adverse events (local and systemic), irAE.

Information sources

An expert librarian searched two electronic databases Ovid Medline and Ovid Embase from December 1, 2019 to February 05, 2022. We also manually reviewed the references in other reviews of COVID-19 vaccination in patients with cancer.

Search strategy

The search included terms related to coronavirus vaccination, cancer, and ICI (online supplemental tables S1 and S2).

We used EndNote V.X9 (Clarivate) to manage references.

Selection process, data collection process and data items

Two reviewers (JIR and MAL-O) independently screened the citations and reviewed the studies of interest for inclusion. Disagreements were resolved by discussion. Data was extracted by one reviewer (JIR) and cross-checked by a second reviewer (MAL-O). The following information was extracted for each included study: (1) general study information (ie, year of publication, country, study design), (2) population characteristics (ie, age, gender, number of patients), (3) intervention characteristics (ie, number of patients under ICI treatment, number of patients in comparison group, interval between COVID-19 vaccine and outcome assessment, types of ICI, types of comparison (chemotherapy, no treatment, healthy individuals) and (4) outcomes: severe disease (according to each publication authors' definition), ICU admission, mechanical ventilation, mortality, seroconversion, rate of irAE and type of irAE.

Study risk of bias assessment

The risk of bias was assessed by two reviewers (JIR and MAL-O) and discrepancies were resolved by discussion. We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of observational studies. This scale consists of three components: patient selection, study comparability, and outcome assessment, with scores ranging from 0 to 9 (best).

Synthesis methods

We performed the statistical analysis using Review Manager V.5.3 (RevMan).

Effect measures

We presented the measure of association as risk ratios (RRs) and their corresponding 95% CI. If the data were not suitable for pooling, we synthesized the results narratively.

Processes used to decide which studies were eligible for synthesis

In order to decide which studies were eligible for each synthesis we specified and tabulated the study

characteristics (population, intervention, the comparisons groups, and the outcomes).

Methods required to prepare the data for synthesis

We calculated the RRs when study provided raw data on frequency of events and sample sizes. We used the Mantel-Haenszel method for meta-analysis of dichotomous raw data. Adjusted estimates were used where possible for primary analyses, to decrease potential confounder bias. Data were pooled using random effects models.

Heterogeneity

We assessed heterogeneity using I^2 statistics. We considered that heterogeneity was present when the I^2 was higher than 40%.

Methods to explore heterogeneity

We grouped studies by type of vaccine, and type of design (prospective vs retrospective) to determine their potential effect on the results.

Additional analyses

In order to evaluate the occurrence of unusual adverse events of ICIs in patients with COVID-19 immunization, we summarized case reports and case series that identified irAE that may not be detected in longitudinal observational studies.

Reporting bias assessment

We planned a priori to assess and quantify publication bias using funnel plots and Egger's test if more than 10 studies reported on the primary outcome. However, data were insufficient to perform this analysis.

Certainty assessment

We evaluated the quality of the evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which considers risk of bias, indirectness, inconsistency, imprecision, and publication bias.[10] We created summary of findings tables (SoF), which synthesize the most important results of a review in a structured format that is transparent providing information about the quality of evidence and the magnitude of the effects of the outcomes of interest, including the following information for each of the important outcomes (desirable and undesirable)[11]: (1) the relative effect of the intervention, (2) the baseline risk (control group), (3) the absolute risk of the intervention group, (3) the number of studies and number of participants, and (4) the confidence in the effect estimates or certainty of the evidence.[12] The RR with its 95% CI was obtained from the meta-analyses performed for each outcome and comparison. The absolute risks for each comparison groups were obtained from the representative studies of the review or the median comparator group risk across studies. The intervention absolute risk was obtained from the following calculation:

$$\textit{absolute risk with the intervention} = \textit{absolute risk with the comparator} \times RR \times 1000$$

The certainty of the evidence was assessed using the specific grading system of the GRADE working group that considers the following domains: (1) risk of bias (ie, the confidence on the estimate of effect decreases because there are limitations in the study design), (2) inconsistency (ie, when the estimates of effect vary widely from one study to the other and there are no explanations for this heterogeneity), (3) indirectness (ie, the estimate of effect comes from studies with different population, and/or intervention, and/or comparison, and/or outcome from our main review question, (4) imprecision (ie, the studies include few number of participants and/or events or the 95% CI includes both benefits and harms for the patients), and (5) publication bias (ie, when investigators do not report studies because of lack of effect or selecting and non-reporting outcomes). The certainty or quality of the evidence was rated as high (indicating that further research is very unlikely to change our confidence in the estimate of effect), moderate (indicating that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (indicating that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (indicating that any estimate of effect is very uncertain).

RESULTS

Search results

The strategy identified 191 citations (figure 1). After removing duplicated studies, we screened 147 citations. We included 37 studies for full text assessment. Finally, 19 studies were eligible to include for analysis.[13–31] A total of 10 865 participants were included in the analysis and 2477 received ICI.

Description of included studies

Study characteristics are described in table 1. Considering the type of studies included, 3 were case reports, 15 cohort studies, and 1 cross-sectional study. The range of ages included were 16–93 and the average of male participants was 52%. The types of vaccines included were: BNT162b2 (Pfizer) in 16 (84%) studies,[13–16 18 20 21 23–25 27–31] mRNA-1273 (Moderna) in 8 (42%) studies,[17–19 25–27 29 30] Ad26.COV2S (Janssen) in 3 (16%) studies,[25 27 30] Sinovac in 1 (5%) studies,[22] Sinopharm in 1 (5%) study,[22] ChAdOx1 nCoV-19 (AstraZeneca) in 1 (5%) study.[27] With regard to the outcomes, 12 studies reported immunogenicity as humoral response 14–30 days after the second dose of the vaccine,[13 16 18–23 25 26 29 30] 10 studies reported irAE,[14 15 17 20 22 24 26 27 29 31] 9 reported vaccine-related adverse events (VrAE),[16 20 21 25 26 28 29 31] and 3 reported incidence of COVID-19.[20 21 29] The characteristics of the participants included in the studies are in table 2. The types of cancer included and the funding information for each study are shown in online supplemental table S3.

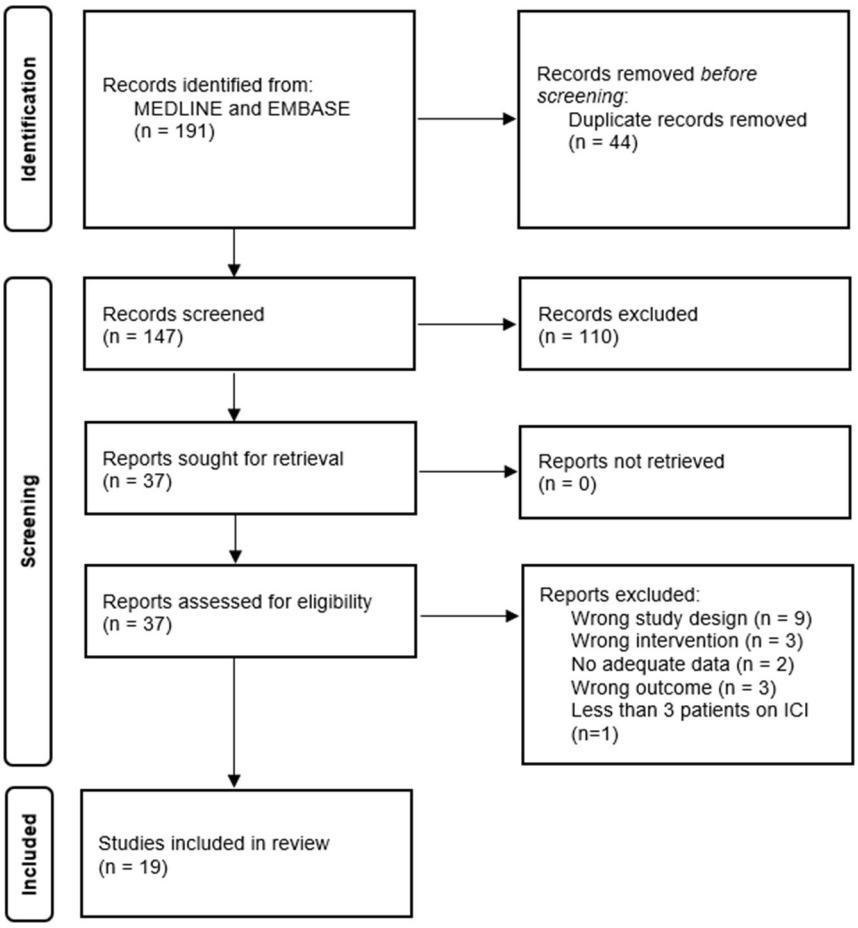

Figure 1 Flow diagram of study selection.

Observational studies

The reported rates of seroconversion and adverse events of individual studies are shown in online supplemental table S4.

Seroconversion

Patients with cancer treated with ICI compared with controls without cancer (figure 2) (7 studies[13 18 21–23 26 30] including 473 patients on ICI and 747 controls). No statistically significant differences were observed in the pooled estimate (RR 0.97, 95% CI 0.92 to 1.03). However, when analyzing the subgroups by type of vaccines, the risk of seroconversion with the inactivated vaccines Sinopharm or Sinovac was lower in patients with cancer treated with ICI compared with individuals without cancer (RR 0.85, 95% CI 0.74 to 0.97).

Patients with cancer treated with ICI compared with patients with cancer treated with chemotherapy (figure 3) (9 studies[13 16 18 19 21 23 25 26 30] including 439 patients on ICI and 778 patients on chemotherapy). The RR for this comparison was 1.09 (95% CI 1.00 to 1.18) favoring patients treated with ICI.

Patients with cancer treated with ICI compared with patients with cancer without active treatment (figure 4). Three studies[16 19 25] reported seroconversion for this comparison including 104 patients on ICI and 228 patients with cancer without active treatment. No statistically significant differences were observed in the pooled estimate (RR 1.00, 95% CI 0.96 to 1.04).

COVID-19 infection

Three studies[20 21 29] evaluated the incidence of COVID-19 infection including 155 patients with cancer treated with ICI. There were no COVID-19 infection cases documented during the period of the studies. As no COVID-19 infections were reported, severity and mortality could not be evaluated.

Vaccine-related adverse events

Ten studies[16 20–22 25–29 31] reported the frequency of VrAE in patients with cancer treated with ICI and who received the COVID-19 vaccine. The results for individual studies are shown in online supplemental table S3. Overall, most of the VrAE were mild or moderate, with local pain and fatigue as the most common VrAE. The range of rate of fatigue was from 24% to 59%, the range of local pain was from 6% to 63%. In one study[22] that used the inactivated vaccines Sinovac and Sinopharm there was a statistically significant difference in rash comparing patients who received ICI vs those who did not receive ICI (OR 3.5, 95% CI 1.67 to 7.35 p<0.001).

Patients with cancer treated with ICI compared with controls without cancer. One study[26] (VOICE trial)

Table 1 Characteristics of included studies

Study ID	Country	Health centers n	Period	Vaccine	Total n	Outcomes	Seroconversion cut-off
Retrospective cohort studies							
Chen *et al* 2021[17]	USA	1	NR	BNT162b2 (Pfizer) and mRNA-1273 (Moderna)	81	irAE, VrAE	–
Ligumsky *et al* 2021[21]	Israel	1	March–April 2021	BNT162b2 (Pfizer)	490	Immunogenicity (humoral response), VrAE	>50 AU/mL
Ma *et al* 2021[22]	China	4	NR	CoronoVac (Sinovac) and Beijing Bio-Institute of Biological Products (Sinopharm)	660	Immunogenicity (humoral response), irAE	–
Strobel *et al* 2021[27]	Germany	1	March–July 2021	BNT162b2 (Pfizer), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), and Ad26.COV2S (Janssen)	130	irAE	–
Svoboda *et al* 2021[29]	USA	NR	July 2020–June 2021	BNT162b2 (Pfizer) and mRNA-1273 (Moderna)	23	Immunogenicity (humoral response), VrAE, irAE	Receptor binding domain >0.700 AU
Prospective cohort studies							
Buttiron-Webber *et al* 2021[16]	Italy	NR	NR	BNT162b2 (Pfizer)	320 (291 analyzed)	Immunogenicity (humoral response), VrAE	>25 AU/mL
Di Giacomo *et al* 2021[18]	Italy	NR	NR	BNT162b2 (Pfizer) for healthy hospital personnel and mRNA-1273 (Moderna) for patients with cancer	173	Immunogenicity (humoral response)	>50 AU/mL
Figueiredo *et al* 2021[19]	USA	1	December 2020–August 2021	BNT162b2 (Pfizer) and mRNA-1273 (Moderna)	1697	Immunogenicity (humoral response)	>50 AU/mL
Lasagna *et al* 2021[20]	Italy	Multi-center	March–April 2021	BNT162b2 (Pfizer)	88	Immunogenicity, incidence of COVID-19, VrAE, irAE	>15 AU/mL
Massarweh *et al* 2021[23]	Israel	1	February–March 2021	BNT162b2 (Pfizer)	180	Immunogenicity (humoral response)	>50 AU/mL
Naranbhai *et al* 2021[25]	USA	1	April–July 2021	BNT162b2 (Pfizer), Ad26.COV2S (Janssen), mRNA1273 (Moderna)	762*	Immunogenicity, VrAE	Index >0.8
Oosting *et al* 2021 (VOICE trial)[26]	Netherlands	Multi-center: 3	February–March 2021	mRNA-1273 (Moderna)	750	Immunogenicity (humoral response), VrAE, irAE	>10 AU/mL
Subbiah *et al* 2021[32]	USA	1	NR	BNT162b2 (Pfizer)	4714	VrAE (Patient reported outcomes)	–
Thakkar *et al* 2021[30]	USA	NR	NR	BNT162b2 (Pfizer), mRNA-1273 (Moderna), Ad26.COV2S (Janssen)	242†	Immunogenicity (humoral response)	>50 AU/mL
Waissengrin *et al* 2021[31]	Israel	1	January–February 2021	BNT162b2 (Pfizer)	268	VrAE, IrAE	–
Cross-sectional studies							
Agbarya *et al* 2021[13]	Israel	Multi-center: 2	February–April 2021	BNT162b2 (Pfizer)	355	Immunogenicity (humoral response)	>150 AU/mL
Case reports							
Au *et al* 2021[14]	UK	NR	December 2020	BNT162b2 (Pfizer)	–	irAE (cytokine release syndrome)	–

Continued

Table 1 Continued

Study ID	Country	Health centers n	Period	Vaccine	Total n	Outcomes	Seroconversion cut-off
Blaise *et al* 2021[15]	France	NR	January 2021	BNT162b2 (Pfizer)	–	irAE (necrotizing myopathy – Grade 4)	–
Mieczkowska *et al* 2021[24]	USA	NR	NR	BNT162b2 (Pfizer)	–	irAE (Psoriasis exacerbation)	–

*Excluding the healthy controls reported in the literature previously.
†200 analyzed for efficacy.
ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; NA, not applicable; NR, not reported; VrAEs, vaccine-related adverse events.

including 137 patients on ICI and 240 controls reported VrAE. No statistically significant differences were observed for the following adverse events: fatigue (RR 1.09, 95% CI 0.91 to 1.31 p=0.36), pain (RR 1.60, 95% CI 0.63 to 4.06 p=0.32), VrAE grade 3 or worse (RR 12.22, 95% CI 0.64 to 234.9 p=0.1).

Patients with cancer treated with ICI compared with patients with cancer treated with chemotherapy. One study[26] including 137 patients on ICI and 244 on chemotherapy reported VrAE. No statistically significant differences were observed for the following adverse events: fatigue (RR 1.21, 95% CI 0.99 to 1.47 p=0.06), pain (RR 1.25, 95% CI 0.52 to 3.03 p=0.62), VrAE grade 3 or worse (RR 0.89, 95% CI 0.23 to 3.50 p=0.87).

Immune-related adverse events

Six studies[17 20 22 26 27 31] reported the frequency of irAE in patients with cancer treated with ICI and who received the COVID-19 vaccine. The results of individual studies are shown in online supplemental table S3. The range of rate of irAE was from 0% to 23.6%. No unusual adverse events were reported.

There was only one study[22] that reported the risk of irAE comparing patients treated with ICI who received the vaccine versus those who did not receive it. This study evaluated the inactivated vaccines Sinopharm and Sinovac including 127 patients on the vaccine group and 127 patients on the non-vaccine group performing a propensity score matched analysis. No statistically significant differences were observed for pneumonitis (RR 0.88, 95% CI 0.33 to 2.31 p=0.79), rash (RR 1.03, 95% CI 0.66 to 1.62 p=0.88), diarrhea (RR 0.82, 95% CI 0.35 to 1.91 p=0.64), arthralgia (RR 0.94, 95% CI 0.51 to 1.75 p=0.86), liver function test abnormalities (RR 1.07, 95% CI 0.55 to 2.06 p=0.85).

Risk of bias

We used the NOS to assess the risk of bias of the 16 observational studies, (online supplemental table S5). The scores ranged from 3 to 8 (maximum score 9). Nine (56%) of the studies[13 16–18 20 27 29 31 32] had high risk of confounding bias as they did not adjust for potential confounders.

Summary of findings

The summary of findings tables with the certainty of evidence of the different comparisons are shown in online supplemental tables S6–8. The absolute benefit of seroconversion in patients with cancer treated with ICI was: (1) 922 per 1000 (between 874 and 970 per 1000) compared with 950 per 1000 in individuals without cancer, (2) 974 per 1000 (between 935 and 1000 per 1000) compared with 974 per 1000 in patients with cancer without active treatment, and (3) 958 per 1000 (between 879 and 1000 per 1000) compared with 879 per 1000 in patients with cancer treated with chemotherapy. The absolute risk of grade 3 or more VrAE in patients with cancer treated with ICI was 8 per 1000 (between 2 and 29 per 1000) compared with 8 per 1000 in patients with cancer treated with chemotherapy.

For all the comparisons and outcomes, the certainty of the evidence was rated as very low because the risk of bias of the primary studies and downgraded for imprecision. We also downgraded the quality of evidence for indirectness because seroconversion was considered a surrogate outcome.

Case reports

We found three case reports[14 15 24] that reported unusual adverse events in patients with cancer treated with ICI who received the COVID-19 vaccine. In the three cases the patients received the BNT162b2 vaccine. One of the patients presented cytokine release syndrome, another patient necrotizing myopathy grade four and the third case exacerbation of psoriasis.

The studies excluded and the reasons for exclusions are presented in online supplemental table S9.

DISCUSSION

To our knowledge, this is the first systematic review evaluating the efficacy and safety of COVID-19 vaccines in patients with cancer receiving ICI. Previous systematic reviews and meta-analyses[33 34] have reported on the outcomes of COVID-19 vaccines in patients with cancer at large, but not specifically in those receiving ICI. Becerrill-Gaitan *et al* showed that patients with cancer were less likely to seroconvert after complete vaccination compared with non-cancer controls (RR 0.69, 95% CI 0.65 to 0.84).[33] Nevertheless, they did not analyze the effect of the different cancer treatment on the efficacy of the vaccine. A narrative review included information in

Table 2 Characteristics of patients included in the studies

Study ID	Age	Types of ICI	Non-ICI interventions	Interval between second vaccine and evaluation of outcome	% of patients with prior COVID-19 infection
Agbarya *et al* 2021[13]	65.3 (mean)	Pembrolizumab, nivolumab, ipilimumab, durvalumab, avelumab, atezolizumab, cemiplimab (n=43)	Chemotherapy (n=73), biological drugs (24), healthy subjects (n=215)*	14 days	NR
Au *et al* 2021[14]	>18†	Anti-PD-1 monotherapy (n=1)	NA	5 days	NR
Blaise *et al* 2021[15]	>18†	Pembrolizumab, nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) (n=1)	NA	10 days (after first vaccine)	NR
Buttiron Webber *et al* 2021[16]	68 (median)	Unspecified ICI (n=21)	Chemotherapy (n=115), hormone therapy (n=70), targeted therapy (n=23), patients with cancer with no active treatment (n=62)	21 days	11.3
Chen *et al* 2021[17]	70 (median)	Pembrolizumab (n=45), nivolumab (n=22), durvalumab (n=6), cemiplimab (n=5), atezolizumab (n=3)	NA	30 days (at least)	NR
Di Giacomo *et al* 2021[18]	NR	Unspecified ICI (n=70)	Chemotherapy (n=28), Targeted therapy (n=23), healthy subjects (n=42),	18 days (median)	0
Figueiredo *et al* 2021[19]	65 (median)	Unspecified vaccinated ICI (n=74)	healthcare workers (n=1245) Unvaccinated patients with cancer (n=54), vaccinated patients with cancer (n=291)	42 days (median)	Vaccinated: 6.2 Unvaccinated: 22.2
Lasagna *et al* 2021[20]	68 (median)	PD-1/PD-L1 (n=88)	NA	21 days	14.8
Ligumsky *et al* 2021[21]	66 (median)	Unspecified ICI (n=55)	Chemotherapy (n=101), Combination (n=104)‡, targeted therapy (n=38), other treatments (n=28)‡, healthy subjects (n=164)*	78 days	NR
Ma *et al* 2021[22]	50.3 (mean)	Nivolumab (n=51), pembrolizumab (n=49), sintilimab (n=76), toipalimab (n=44), tislelizumab (n=31), camrelizumab (n=39). Patients were divided in PD-1 vaccinated (n=138) and PD1 unvaccinated (n=152)	Patients with cancer without PD-1 (n=164), non-cancer patients (n=206)	1–3 months	NR
Massarweh *et al* 2021[23]	66 (median)	Unspecified ICI (n=22)	Chemotherapy (n=30), chemotherapy plus biological therapy (n=20), biological therapy (n=11), healthy subjects (n=78)	38 days	NR
Mieczkowska *et al* 2021[24]	> 18†	Nivolumab (n=1)	NA	7 days (after first dose)	NR
Naranbhai *et al* 2021[25]	66 (median)	Unspecified ICI (n=70)	No systemic treatment (n=205), healthy subjects (n=418), chemotherapy (n=101), targeted therapy (n=149), combination (n=124)	7 days	
Oosting *et al* 2021 (VOICE trial)[26]	66 (median)	Nivolumab (n=66), pembrolizumab (n=36), cemiplimab (n=7), atezolizumab (n=5), avelumab (n=5), duvalumab (n=2)	Chemotherapy (n=229), chemotherapy plus immunotherapy (n=143), healthy patients (n=247)	28 days	NR

Continued

Table 2 Continued

Study ID	Age	Types of ICI	Non-ICI interventions	Interval between second vaccine and evaluation of outcome	% of patients with prior COVID-19 infection
Strobel *et al* 2021[27]	64 (median)	Pembrolizumab (n=45), nivolumab (n=14), cemiplimab (n=4), avelumab (n=6), combination ICI (n=20)	Non-ICI systemic therapies (n=108), unvaccinated patients with cancer (n=19)	84 days	NR
Subbiah *et al* 2021[32]	54 (median)	Unspecified ICI (n=857)	NA	NR	NR
Svoboda *et al* 2021[29]	42 (median)	PD-1 (n=23)	NA	–	26
Thakkar *et al* 2021[30]	67 (median)	Unspecified ICI (n=31)	Non-cancer patients (n=26), non-ICI treatments (n=169)	7 days	11
Waissengrin *et al* 2021[31]	72 (median)	Unspecified ICI (n=97)	Healthy subjects (n=134)	19 days	NR

*Patients' relatives, healthcare workers, and volunteers.
†Exact patient age not provided as required by the journal.
‡Includes patients receiving other treatments plus ICI.
ICI, immune checkpoint inhibitor; NA, not applicable; NR, not reported; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

patients treated with ICI suggesting that efficacy and safety were similar to that observed in the general population.[7]

The results of our systematic review suggest that COVID-19 vaccines are effective in patients with cancer treated with ICI, as determined by seroconversion rates. We found no significant differences in the rate of seroconversion after the second dose of the vaccine when comparing patients with cancer receiving ICI versus healthy participants. However, the frequency of seroconversion with the inactivated vaccines Sinopharm or

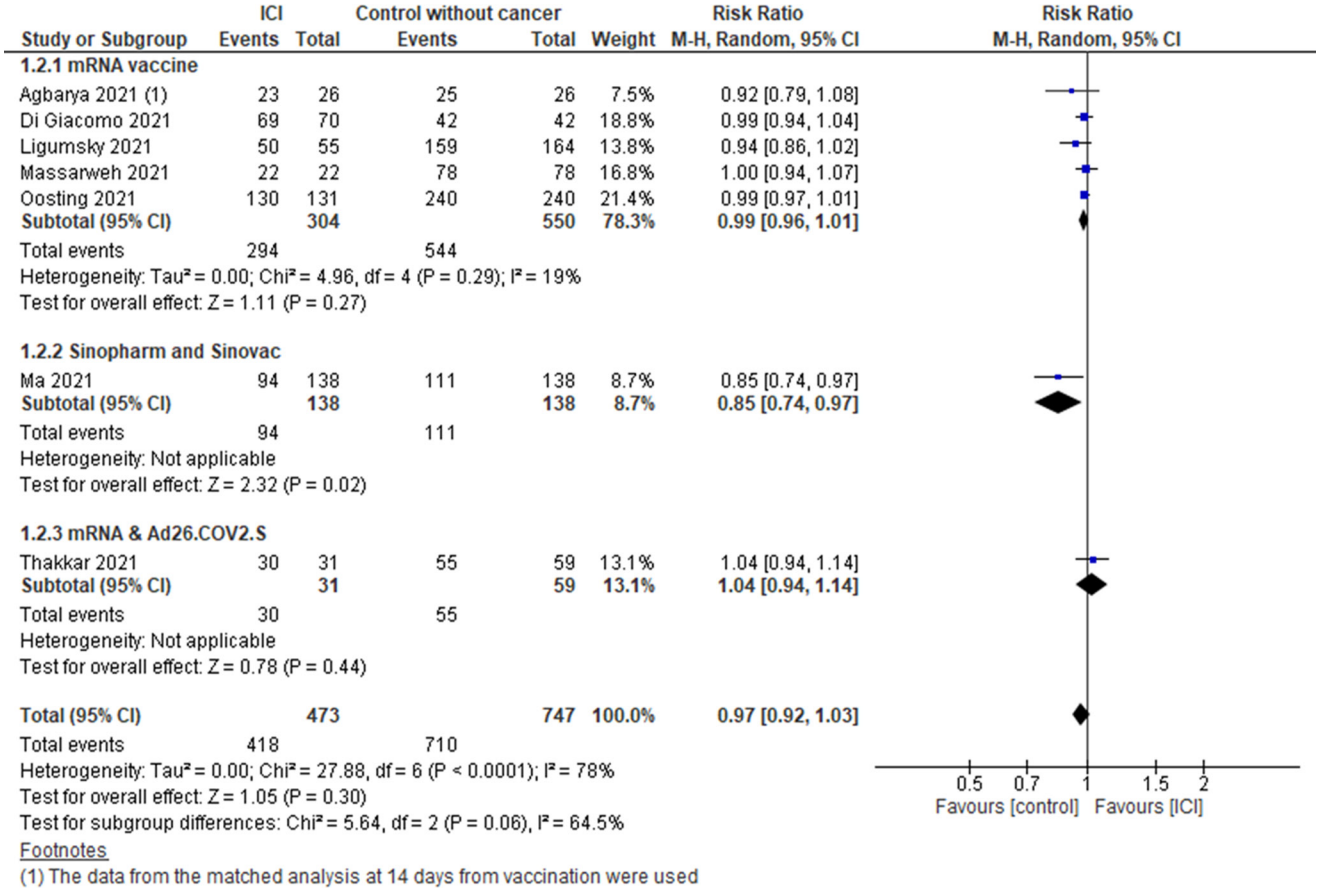

Figure 2 Risk of seroconversion after COVID-19 vaccination in patients with cancer treated with ICI versus control without cancer. ICI, immune checkpoint inhibitor.

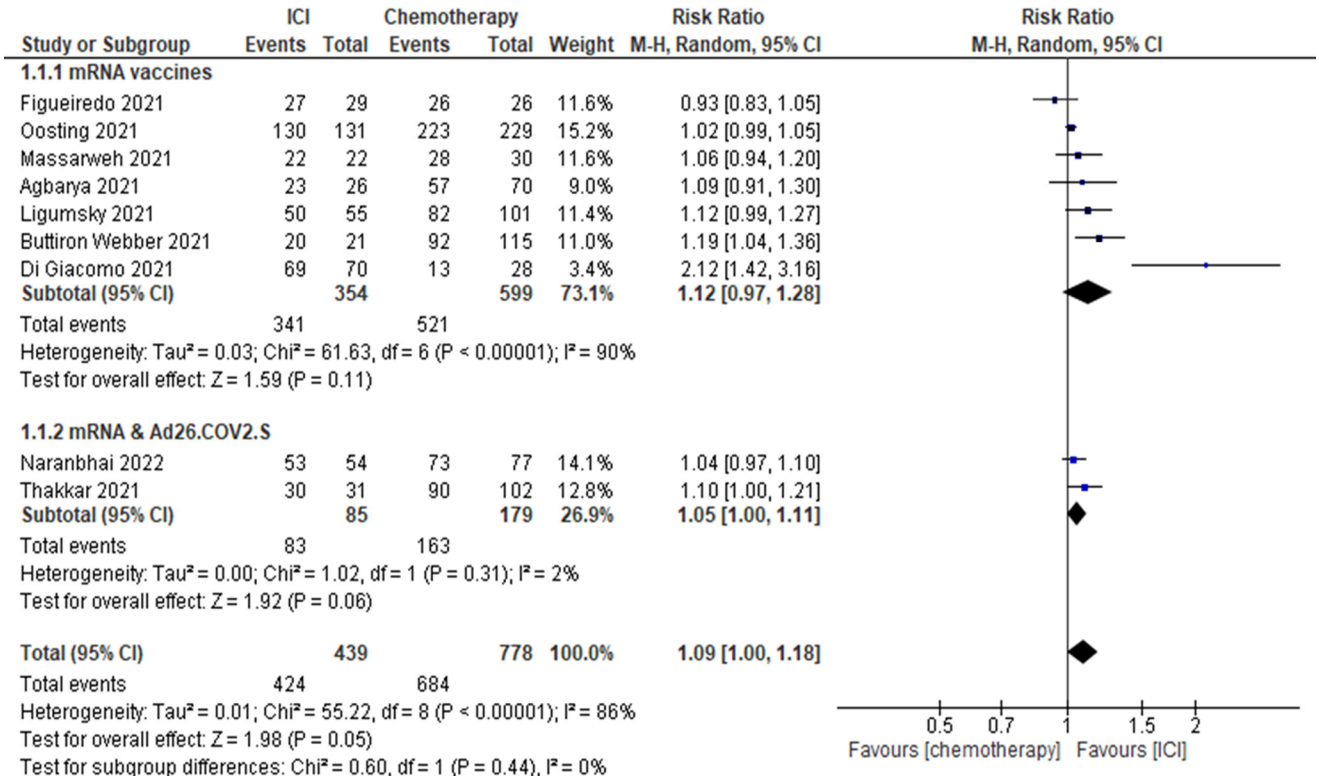

Figure 3 Risk of seroconversion after COVID-19 vaccination in patients with cancer treated with ICI versus patients with cancer treated with chemotherapy. ICI, immune checkpoint inhibitor.

Sinovac was significantly lower in patients with cancer treated with ICI compared with individuals without cancer. Patients with cancer treated with ICI showed a higher probability of seroconversion than patients with cancer treated with chemotherapy. Rates of COVID-19 infection were evaluated in three small studies, and none of the 155 patients receiving ICI developed COVID-19. Therefore, the impact of vaccination on clinically important outcomes such as hospital admissions, use of mechanical ventilation or death, could not be assessed.

As treatment with ICI enhances immune responses, there have been theoretical concerns that concomitant treatment with ICI and receipt of the COVID-19 vaccination, could result in increased risk of irAE.[6] Only one study[22] reported irAE comparing patients on ICI who received the inactivated vaccines Sinopharm and Sinovac vaccines with those who did not receive vaccination, and found no statistically significant differences between the two groups. Other studies reported rates of irAE with mRNA vaccines, ranging 0%–24%, but they did not have

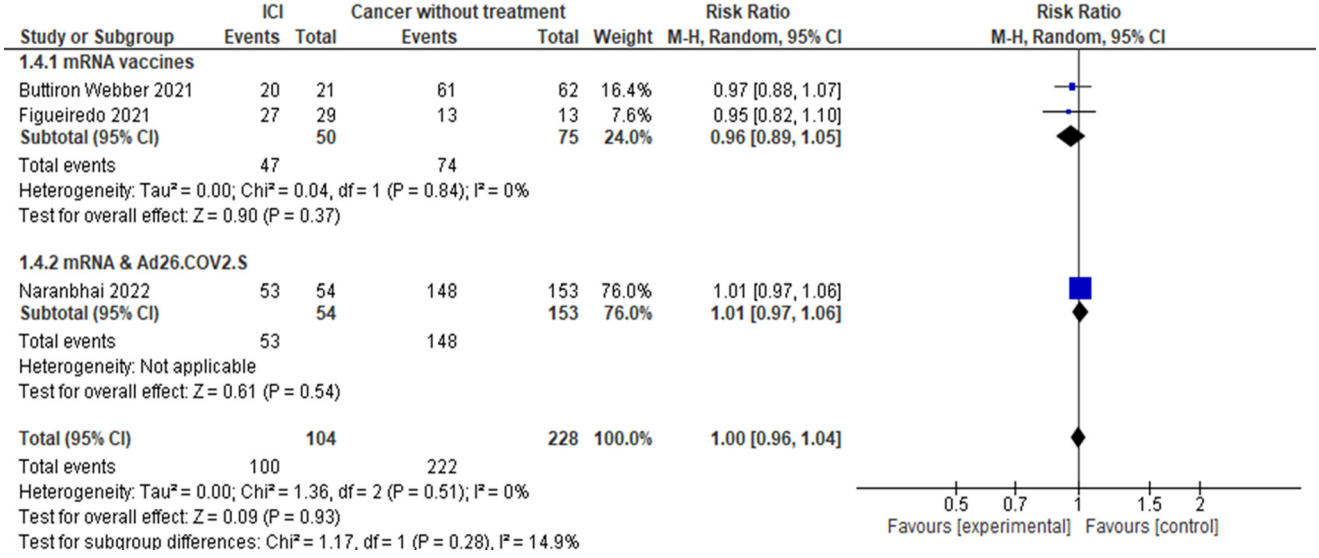

Figure 4 Risk of seroconversion after COVID-19 vaccination in patients with cancer treated with ICI versus patients with cancer without treatment. ICI, immune checkpoint inhibitor.

suitable control groups of unvaccinated patients receiving ICI. These rates, however, seem similar to the observed rates of irAE in studies of patients receiving ICI (not related to vaccination).[35–37] Moreover, most of the irAE were low grade. No unusual adverse events were reported in these studies.

With regard to the adverse events related to the vaccination, most of them were local pain and fatigue with a range of 6%–63% and 24%–59%, respectively. Most of the VrAE reported were mild or moderate. In the study of patients who received the inactivated vaccines Sinovac and Sinopharm[22] there was a higher risk of developing rash in patients treated with ICI compared with those not treated with ICI. The VOICE trial[26] that evaluated the safety and efficacy of the mRNA-1273 vaccine in patients with cancer, showed no statistically significant differences on VrAEs in patients treated with ICI compared with participants without cancer, or patients with cancer treated with chemotherapy. Only 3 of 137 patients treated with ICI (2%) in this study had grade 3 or more VrAE. Another study showed that the patients who received ICI reported a higher increase of itch and rash after receiving the second dose of the mRNA vaccine compared with those without cancer treatment.[32] However, this was reported in a conference abstract and no frequencies were provided.

This systematic review provides the most recent synthesis of evidence about the efficacy and safety of COVID-19 vaccines in patients with cancer receiving ICI. However, it had limitations inherent to the evidence that was available for review and synthesis. The certainty of the evidence in our systematic review was rated as low or very low for all the outcomes evaluated. We rated down for risk of bias and for imprecision. As we stated before, none of the studies evaluated critical outcomes (ie, mortality, several COVID-19, hospital admission). We consider seroconversion as a surrogate outcome and we rated down the certainty of evidence for indirectness.[38] Another limitation, is the information provided regarding to the differences in ICI, regimen, and dose and duration of ICI across the studies. Among the 16 cohort studies included, 11 (69%) did not specify the ICI used or the specific regimen (monotherapy or combination therapy). These factors might have an impact on the outcomes of interest, as it has been shown that dose and duration of ICI might affect the rate of irAE in general.[39] Moreover, combination therapy has a higher risk of irAE compare to monotherapy.[40] Since the primary studies of this systematic review are not randomized control trials, there are several other known and unknown confounding factors that could have an impact on the results as the compared groups may not be balanced, risk factors were not adjusted for in the analyses. Some potential confounders include demographics, prior comorbidities including history of autoimmune disorders, prior cancer treatment or concurrent medications which could impact the development of irAE.[39 41]

In summary, the efficacy of the COVID-19 vaccination in patients with cancer treated with ICI, measured by seroconversion, was similar to that of healthy controls and higher than that observed in patients with cancer who received chemotherapy. No increase in VrAE or irAE were reported. Our results suggest that COVID-19 vaccination seems effective and safe in patients with cancer receiving ICI, although higher-quality evidence may be needed to further establish the robustness of these findings, including observational studies with low risk of bias and evaluating clinical important outcomes of vaccination such as COVID-19 incidence and severity, and related hospitalization and mortality.

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Contributors MES-A conceived the idea of the study. MES-A and JIR developed the protocol. YG performed the literature search. JIR and MAL-O reviewed and appraised the data. JIR and MAL-O conducted the analysis. JIR, MAL-O, YG and MES-A participated in writing the manuscript.

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