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RESEARCH ARTICLE

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Seroconversion rate after COVID-19 vaccination in patients with solid cancer: A systematic review and meta-analysis

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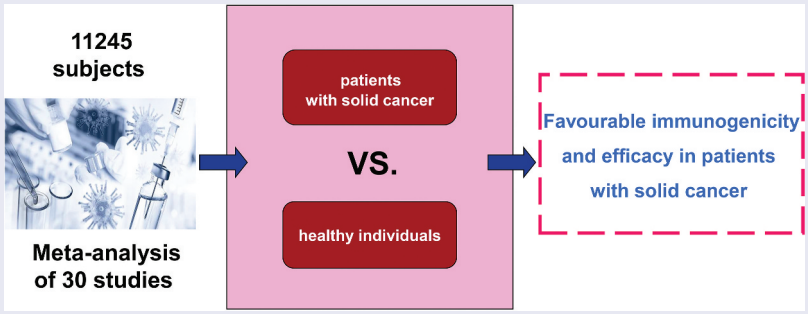
ABSTRACT

Patients with solid cancer have an increased risk of severe coronavirus disease 2019 (COVID-19) and associated mortality than the general population. This meta-analysis aimed to investigate the currently available evidence about the efficacy of COVID-19 vaccines in patients with solid cancer. We included prospective studies comparing the immunogenicity and efficacy of COVID-19 vaccines between patients with solid cancer and healthy individuals. Relative risks of seroconversion after the first and second dose of a COVID-19 vaccine were separately pooled with the use of random effects meta-analysis. Thirty studies with 11,245 subjects met the inclusion criteria. After first vaccine dose, the pooled RR of seroconversion in patients with solid cancer *vs* healthy individuals was 0.54 (95% CI 0.38–0.78, $I^2 = 94\%$). After a second dose, the pooled RR of seroconversion in patients with solid cancer *vs* healthy controls was 0.87 (0.86–0.88, $I^2 = 87\%$). Our review suggests that, compared with healthy individuals, COVID-19 vaccines show favorable immunogenicity and efficacy in patients with solid cancer. A second dose is associated with significantly improved seroconversion, although it is slightly lower in patients with solid cancer compared with healthy individuals.



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COVID-19; SARS-CoV-2; vaccine; solid cancer; immunogenicity; meta-analysis

Introduction

Transmission of SARS-CoV-2 has led to the ongoing global COVID-19 pandemic. By July 2022, more than 518 million have had confirmed COVID-19 and more than six million have died worldwide. In addition to large-scale economic disruption, COVID-19 has caused various manifestations in multiple organ systems,[1–5] and has increased disease severity and mortality in patients with solid cancer.[6–11]

Among the proposed novel treatment strategies,[12–17] vaccination is the most effective strategy for preventing SARS-CoV-2 infection.[18] Fortunately, a concerted global effort has prompted an unprecedented pace in several highly effective vaccines development.[19–21] All of these vaccines were well tolerated in clinical trials and their proven efficacy was greater than 90% in preventing symptomatic laboratory-confirmed SARS-CoV-2 infection, except for the CoronaVac vaccine, which only had proven efficacy of 51%.[22–25] In many parts of the world, mass vaccination campaigns have considerably reduced the incidence of severe COVID-19 in the general population after at least two vaccine doses. Vaccine trials, however, have excluded patients with solid cancer, leading to a paucity of data on the efficacy and safety of currently available vaccines as well as the durability of vaccine responses remain in this population. Owing to the increased risk of COVID-19-related complications and mortality, patients with solid cancer were prioritized for vaccination.[26–28] These patients, which comprise only a minority of the global population, are of particular interest because of possible suppression or over-activation of the immune system attributable to the primary disease or concurrent treatment.[29] Data are urgently needed on patients with solid cancer, as infection and viral shedding have been reported to be more severe and persistent in this group.[30–32]

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This systematic review and meta-analysis aims to integrate the currently available evidence to assess the serologic response rate of COVID-19 vaccines in patients with solid cancer. Better understanding the overall efficacy of COVID-19 vaccines in solid cancer patients can improve clinical practice and protect this vulnerable patient group.

Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[33]

Search strategy and selection criteria

A comprehensive electronic search (from inception to 30 May 2022) of PubMed/Medline, EMBASE, the Cochrane Library database, COVID-19 Open Research Dataset Challenge (CORD-19), and WHO COVID-19 databases was conducted to identify studies assessing the response to COVID-19 vaccination in patients with solid cancer.

We included prospective studies reporting the outcomes of COVID-19 vaccination in patients with solid cancer. No geographic or language restrictions were imposed. There were no restrictions regarding age, sex, or duration of the study. Studies reporting outcomes in patients with active or history of cancer were eligible. The databases were searched (JY) using the mapped terms ["cancer" OR "tumor" OR "malignancy"] AND "vaccine" AND ["COVID-19" or "SARS-CoV-2"] and the exploded MeSH terms "COVID-19 Vaccines." To improve the validity of data, we excluded non-peer reviewed articles in preprint databases. The reference lists of all included articles were also manually searched to identify any potentially eligible studies.

Two reviewers double-screened independently each title and abstract (JY and CW). Discrepancy or uncertainty was resolved by a third independent reviewer (YL). Studies were limited to human participants and of any follow-up duration and time points.

We performed a meta-analysis of prospective studies that met the following criteria: human participants who received a COVID-19 vaccine of any brand and type; patients with solid cancer; studies that included and reported data on a control group comprising subjects who are not with solid cancer; and studies that reported at least one of seroconversion after COVID-19 vaccination or serological titers after COVID-19 vaccination.

We excluded studies that enrolled but did not report outcomes of a control group; reported seroconversion data in a form that prevented the calculation of proportions, risk of seroconversion, or number of seroconverted participants; and reported serological titers in a form from which neither mean nor median titers could be derived.

When studies did not provide available data, we contacted the corresponding authors via e-mail for information. We excluded studies only if data were not provided at the time of meta-analysis.

Data extraction

Two reviewers (JY and CW) synthesized data from all eligible studies and created graphs using a Microsoft Excel spreadsheet. At the end of the data extraction phase, all key extracted data were reviewed and quality checked by the same two reviewers.

Risk of bias assessment

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to rate risk of bias for non-randomized included studies. This tool assesses seven domains: risk of bias from confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.[29] Two investigators (JY and CW) independently judged these domains as low, moderate, serious, or critical risk of bias, or no information. All discrepancies were first discussed between the investigators, then split by a third investigator (×S) in case of persistent discordance. A study would be judged as having an overall low risk of bias if all the domains were judged as low risk. A study would be considered as having critical risk of bias if one domain was judged at high risk of bias. A standardized method, namely, version 2 of the Cochrane risk-of-bias tool (RoB 2) was to be used for randomized trials.[34] During this study, however, no eligible randomized studies were found.

Outcome assessment

The primary endpoint was seroconversion after a first and second dose of SARS-CoV-2 vaccination in patients with solid cancer. As brand and type of assay, type of immunoglobulin, and definition of seroconversion differed across studies, Table 1 reports the respective data for each included study. Secondary outcomes of interest were mean or median serological titers and cumulative incidence of seroconversion after a first and second dose of COVID-19 vaccines. As the type of antibodies measured and reported differed across studies, Table S1 and S2 show the titers after a first and second vaccine dose, respectively. The time points of serological assessment after COVID-19 vaccination and the different brands of serological kits are shown in Table 1. Subgroup analyses according to proportion of patients on anti-cancer medication/treatment and age of subjects were undertaken when data were available. Anti-cancer medications/treatments included chemotherapy, monoclonal antibodies, immune check-point inhibitors, radiotherapy, hormonal therapy, etc. were assessed separately.

Statistical analysis

We used random effects model to estimate the pooled risk ratios (RR) and corresponding 95% confidence intervals (CI) for the primary outcomes of interest. A RR < 1 indicates that patients with solid cancer had a lower risk of achieving seroconversion after COVID-19 vaccination compared with control groups. Statistical heterogeneity of the results in the enrolled studies was assessed by χ^2 test and I^2 statistic. We

Table 1. Characteristics of included studies.

Descriptions of included studies						Outcomes available for analysis				
N	Study	Funding	Design	Main criteria	inclusion N	Definition of remission	Definition of response		Induction of Remission wk	Induction of Response wk
1	Chen 2020	Yes	RCT	CDAI＞220 Anti-TNF naive	102	CDA＜150	ΔCDAI＞70	ΔCDAI＞100	4	4
2	Hanauer 2006	Yes	RCT	CDAI＞220 Anti-TNF naive	225	CDA＜150	ΔCDAI＞70	ΔCDAI＞100	4	4
3	Sandborn 2007	Yes	RCT	CDAI 220–450, IFX resistant	159	CDA＜150	ΔCDAI＞70	ΔCDAI＞100	4	4
4	Watanabe 2012	Yes	RCT	CDAI＞220	67	CDA＜150	ΔCDAI＞70	ΔCDAI＞100	4	4

Abbreviations: RCT: randomized controlled studies; and CDAI: Crohn's disease activity index; IFX: Infliximab.

considered heterogeneity to be significant when the *P* value <0.10, or the I^2 statistic was ≥50%.[35]

We performed separate meta-analyses for the relative risk of seroconversion (measured as RR compared with healthy controls) after each vaccine dose. Generalized linear mixed effects models were used to pool the logit transformed proportions of patients with solid cancer who achieved seroconversion after a first and second COVID-19 vaccine dose.

Statistical analyses were performed using RevMan 5.4 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020). Unless specified otherwise, we considered a two-sided *P* value of <0.05 to be statistically significant.

Publication bias was assessed by the visual inspection of funnel plot.[36] We performed subgroup analysis to determine if the results were influenced by the type of COVID-19 vaccines. Sensitivity analysis was conducted to assess the robustness of the synthesized results.

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[37]

Results

Study characteristics

Thirty articles including 11,245 subjects met eligibility criteria (Figure 1) and were included for meta-analysis of seroconversion rates (Table 1).[38–67] Tables S1 and S2 present the serological antibody titers after a first and second dose of COVID-19 vaccines, respectively. In addition, four articles that met the inclusion criteria for meta-analysis were excluded because seroconversion rates among healthy controls could not be obtained in time from the corresponding authors.[68–71]

In the 34 included studies, 32 (94.1%) used mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), in which eight (23.5%) studies used simultaneously with viral vector vaccines AZD1222 (ChAdOx1 nCoV-19; Oxford-AstraZeneca) and Ad26.CoV2.S (Janssen/Johnson & Johnson); and two (5.9%) inactivated vaccines CoronaVac (Sinovac, Biotech). Among the mRNA vaccines, BNT162b2 was used in 30 (88.2%) studies and as the sole vaccine in 16 (47.1%), and mRNA-1273 was used in 15 (44.1%) studies and as the sole vaccine in two (5.9%), therefore BNT162b2 featured more prominently.

Vaccine response

As shown in Figure 2, five studies reported seroconversion after a first vaccine dose in patients with solid cancer (n = 497) compared with healthy controls (n = 898). There was significant difference in the seroconversion rate between patients with solid cancer and healthy controls after a first vaccine dose (RR 0.54, 95% CI 0.38–0.78, I^2 = 94%) (moderate certainty of evidence).

All 30 studies (5,031 patients with solid cancer and 6,214 healthy controls) assessed the serologic response after the second dose of COVID-19 vaccine in patients with solid cancer (Figure 3). The seroconversion rate was lower among patients with solid cancer than that among healthy controls after a second vaccine dose (0.89 [0.86–0.92], I^2 = 87%) (moderate certainty of evidence).

Only two prospective observational studies reported data after a third dose of COVID-19 vaccine, and both used mRNA vaccines as a third dose (Figure 4). There was no significant difference in the pooled RR of seroconversion rate between patients with solid cancer and healthy controls after a third vaccine dose (RR 0.76, 95% CI 0.50–1.14, I^2 = 0%) (moderate certainty of evidence).

Heterogeneity after the second doses

All the five studies reported seroconversion rates among patients with solid cancer after a first dose of COVID-19 vaccine used only mRNA vaccines. Therefore, subgroup analysis was only performed for studies involving mRNA vaccines and non-mRNA vaccines after the second dose. There were significant differences (P < .01 for test of subgroup effect, Figure 5) in effects on seroconversion among mRNA vaccines (risk ratio 0.88, 0.84 to 0.92), mRNA mixed with viral vaccines (0.92, 0.86 to 0.98), and inactivated vaccines (0.71, 0.43 to 1.18).

The brand of serology kit for assays and country/region of study were of inconsistent significance across patients with solid cancer groups, and are therefore unlikely to be major confounders overall.

Mixed effects meta-regression of seroconversion against potential effect moderators (continuous and categorical study level characteristics), including country/region, race, mean age of patients, brand of serology kit, time points for assays after COVID-19 vaccination, and risk of bias of study showed no

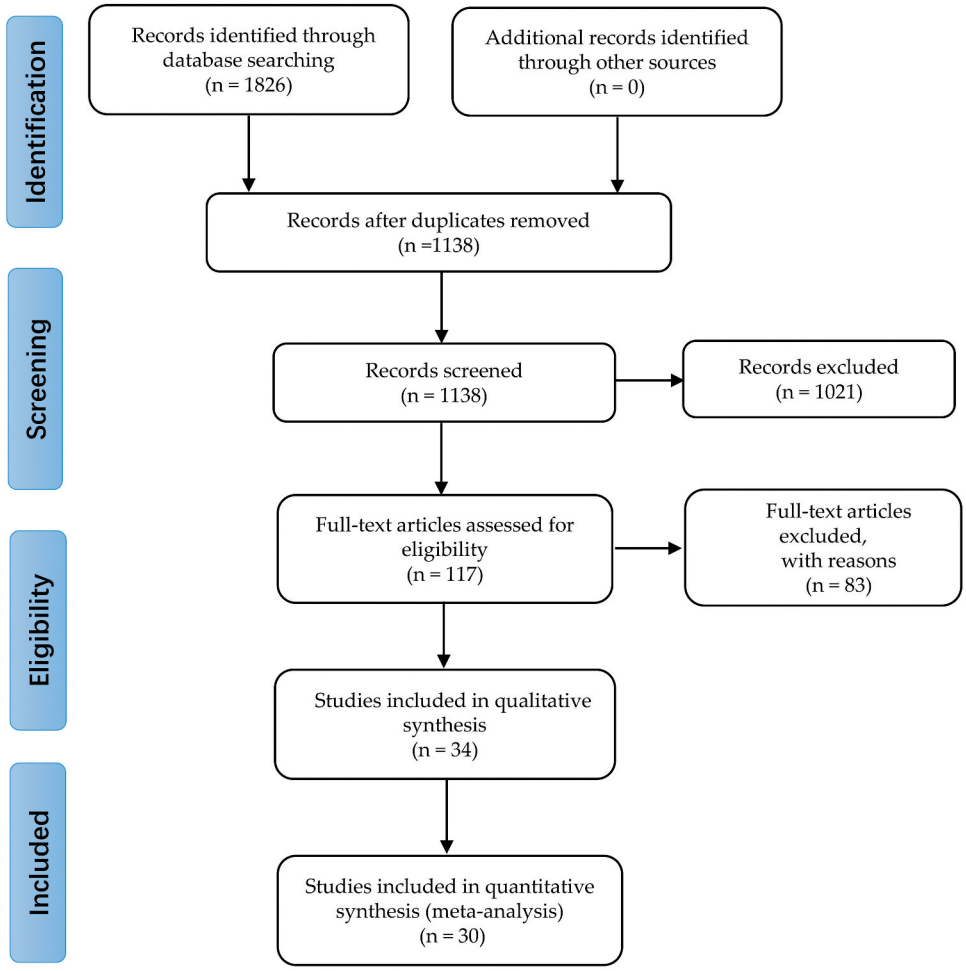

Figure 1. Flowchart of study selection.

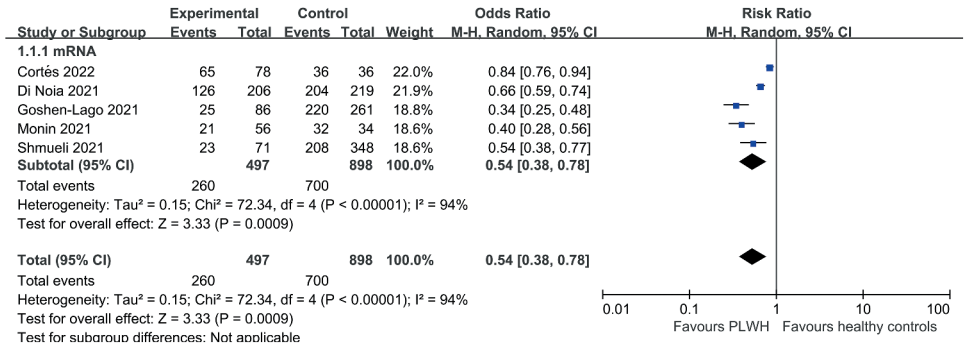

Figure 2. Pooled risk ratios for patients with solid cancer compared with healthy controls after a first dose of COVID-19.

consistent effect moderation across patients with solid cancer after the second dose.

Risk of bias assessment

Twenty-three studies were assessed to be at low risk of bias and seven at moderate risk of bias (Table S3). No studies were considered at severe or critical risk of bias. Risk of bias was mainly associated with confounding effects or with controls not being age-matched.

Publication bias

Funnel plot of the studies included in the meta-analysis demonstrated no asymmetry by visual inspection. Therefore, no significant publication bias was found in our study (Figure S1).

Discussion

This meta-analysis was the first to assess and compare the efficacy of COVID-19 vaccines available at present for patients

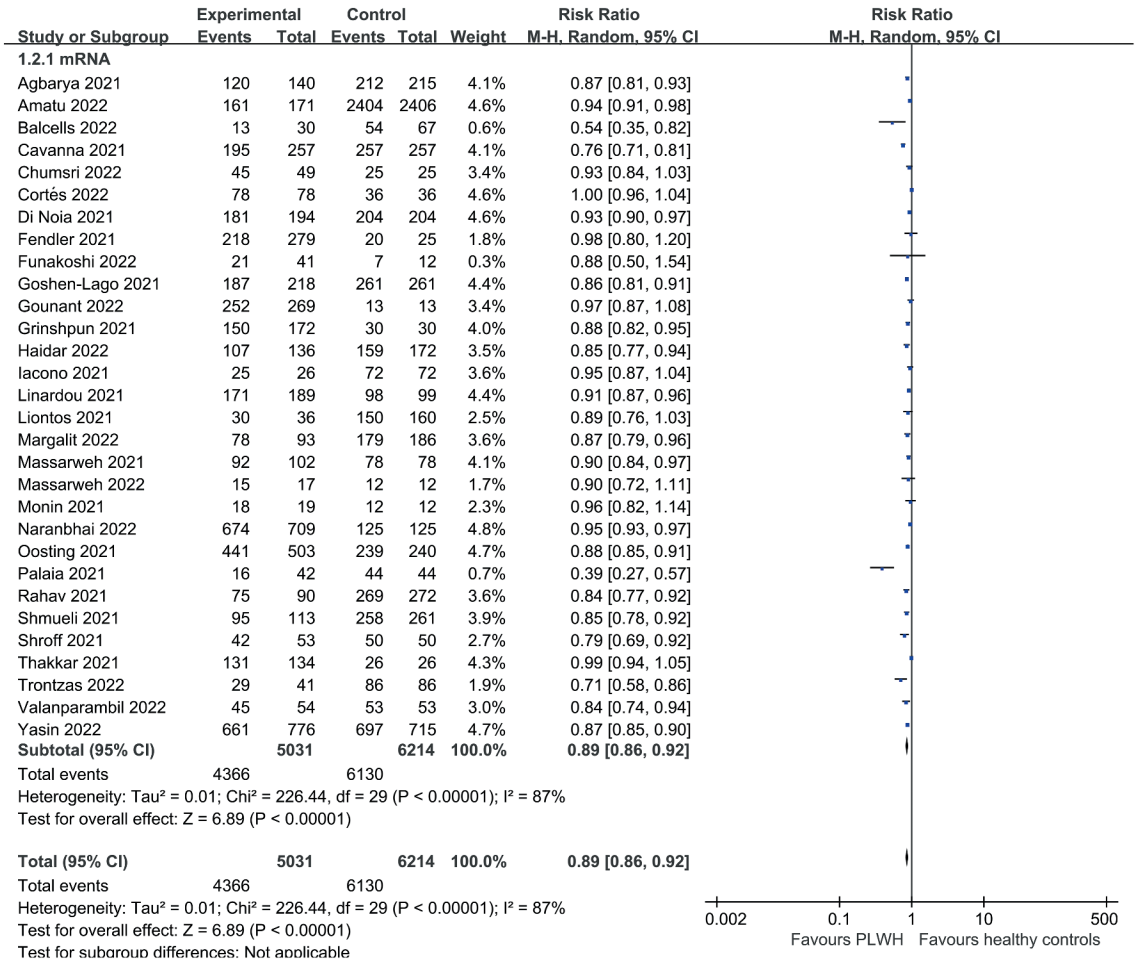

Figure 3. Pooled risk ratios for seroconversion among patients with solid cancer compared with healthy controls.

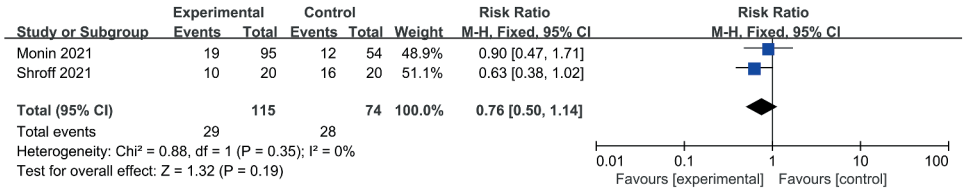

Figure 4. Subgroup analysis of vaccine type among patients with solid cancer patients after first dose.

with solid cancer. In this systematic review and meta-analysis of 30 studies, we found that patients with solid cancer, compared with healthy controls, had a nearly half seroconversion rate after a first dose of COVID-19 vaccine (0.54[0.38–0.78], I^2 = 94%), and seroconversion rates significantly increased after a second dose of COVID-19 vaccine (0.89[0.86–0.92], I^2 = 94%). Among patients with solid cancer, our results cannot show an ideal seroconversion rate even after a second dose of COVID-19 vaccine, prompting the requirement for additional measures. Encouragingly, there was no significant difference in the seroconversion rate between patients with solid cancer and healthy controls after a third vaccination (RR 0.63, 95% CI 0.32–1.24, I^2 = 56%). Shmueli *et al* showed that the booster of BNT162b2 vaccine may be efficacious in eliciting an antibody response in patients with solid cancer who remain seronegative despite two doses of BNT162b2.[72]

Our meta-analyses show significant heterogeneity in immunogenicity between different patients with solid cancer groups after the second dose of COVID-19 vaccines. After the vaccination, the response noticeably varied in patients with solid cancer, which may be attributed to age, ethnicity, sex, smoking, the cancer types, comorbidities, treatments received, quantitative methods used in the studies, measurement kits, and cutoff points to determine a positive seroconversion.[73–75]

To date, there is no international consensus on measures to determine immunogenicity. Surrogate measures, including seroconversion rates and geometric mean titers, were reported in many trials.[76] These surrogate measures involved parameters related to anti-SARS-COV-2 recombinant spike, receptor binding domain (RBD), neutralizing IgG or total antibodies. The use of immunomarkers to reflect the complexity and durability of protective immunity against COVID-19

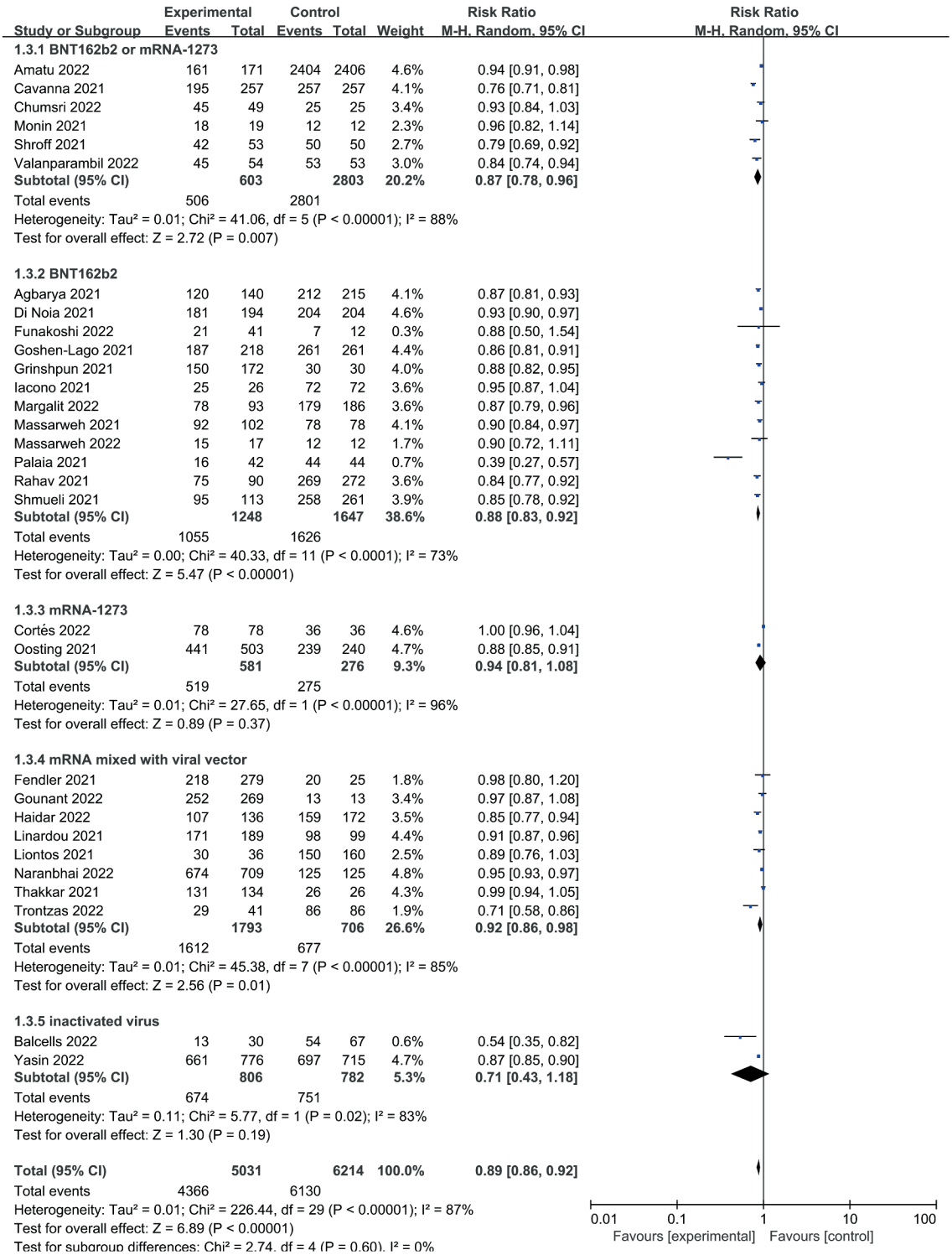

Figure 5. Subgroup analysis of vaccine type among patients with solid cancer patients after second dose.

has been the subject of much debate.[77–82] The neutralizing antibody (NAb) level has more recently been recognized as a reliable predictor of protection against symptomatic COVID-19. However, the measures taken in many studies varied. In this systematic review, only studies that compared measures of effect between patients with solid cancer and healthy controls were enrolled.

In the general population, the adaptive immune response to SARS-CoV-2 consists of T cells that support antibody production while also directly killing virus-infected cells, and B cells that produce different classes of antibodies in order to neutralize the virus.[83] Although memory B and T cells have been described both in naturally infected individuals and in vaccinated populations, their specific roles in achieving protective immunity remain to be determined.[84–86] However, T cells are considered to play a crucial part in reducing the severity of COVID-19.[87–89] Several observational studies suggest that early SARS-CoV-2 *T*-cell responses are associated with milder COVID-19.[88,89] In this regard, data from

a phase III clinical trial investigating COVID-19 vaccines suggest that protection may require low levels of neutralizing antibodies and might involve other immune effector mechanisms, including non-neutralizing antibodies, T cells and innate immunity.[86] Circulating antibody titers did not predict *T*-cell memory.[85,87,90] Furthermore, real-world data indicate that vaccine protection against SARS-CoV-2 infection wanes over time. However, protection against hospitalization and severe disease appears to remain.[91–93] Figuring out the complexity of a protective immune response against SARS-CoV-2 is challenging for patients with solid cancer, given both the biological differences among cancer types and the different treatments received.[94] Additionally, patients with solid cancer have been largely excluded from phase III clinical trials testing vaccine candidates, thus evidence about protective immune responses came from highly heterogeneous single-center observational studies.

Javadinia et al. confirmed that inactivated vaccine is safe and effective in patients with malignancies,[95,96] and that vaccination against COVID-19 in patients with active malignancies using activated or inactivated vaccines is a safe, tolerable, and highly effective procedure.[97] Over the last decade, mRNA has emerged as a promising platform for developing vaccines against infectious disease and cancer.[98] Compared with traditional vaccines such as live attenuated vaccines, inactivated virus vaccines, and protein subunit vaccines, mRNA vaccines have the advantages of versatility, rapid development, good safety profiles, and potent immunogenicity.[99–101] Therefore, multiple researchers and companies have chosen this platform to develop vaccines against COVID-19. It is difficult to directly compare the seroconversion rates of the COVID-19 mRNA vaccines with more traditional, frequently used vaccines. In our study, no significant difference was found in a subgroup analysis of mRNA vs. conventional vaccines in patients with solid cancer. Fan et al. concluded that two mRNA vaccine doses prevent SARS-COV-2 infection most effectively than non-replicating viral vector or inactivated vaccines. However, mRNA vaccines showed more relevance to serious adverse events (SAEs) than the other two vaccine platforms.[102]

This study has several limitations. First, most of the enrolled studies are observational, but one is randomized controlled trial. Factors that might influence the immune response to the vaccine, such as differences in study design and sample size, may not be controlled for between patients with solid cancer and the healthy control group. To address this limitation, we performed a subgroup analysis and found no significant effect modification between studies of different designs. Second, in our study, the seroconversion rate was pooled after the first and second doses of a COVID-19 vaccine. However, the seroconversion rate, an indicator of an immune response to a vaccine, is only a proxy for the effects of the vaccine on infection rate and COVID-19 severity. Data on clinical efficacy endpoints, such as the COVID-19 infection rate in vaccinated patients with solid cancer, are still lacking. Last, the results may be imbalanced, because 20 of the 30 publications enrolled were on mRNA and other eight were mRNA mixed with viral vector. However, in view of the fact that the studies included in this review predominantly used mRNA vaccines, the possible differential analyses were limited.

Conclusions

In conclusion, this meta-analysis has shown that, compared with healthy individuals, COVID-19 vaccines show favorable immunogenicity and efficacy in patients with solid cancer. A second dose was associated with improved seroconversion, although it is slightly lower in patients with solid cancer compared with healthy individuals. Additional strategies, such as the administration of a third (booster) vaccination with mRNA COVID-19 vaccines, might improve seroprotection for these patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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