

RESEARCH ARTICLE

Impaired serological response to COVID-19 vaccination following anticancer therapy: A systematic review and meta-analysis

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Abstract

Owing to the high coronavirus disease 2019 (COVID-19)-related morbidity and fatality rate among patients with cancer, the introduction of COVID-19 vaccines is of profound significance in this fragile population. Accumulating data suggested that oncologic patients, especially those with anticancer therapy have an impaired immune response to COVID-19 vaccination. However, the exact effect of anticancer treatments on postvaccination response has not been elucidated yet. We, therefore, conducted a meta-analysis to evaluate the impact of treatments on response to COVID-19 vaccination in patients with cancer. A total of 39 studies were finally included comprising 11 075 oncologic patients. Overall, we found the humoral response was significantly decreased in patients undergoing anticancer treatments (odds ratio [OR] = 2.55, 95% confidence interval [CI]: 2.04–3.18) compared with those without active treatment. The seroconversion rates were significantly lower in patients with chemotherapy (OR = 3.04, 95% CI: 2.28–4.05), targeted therapy (OR = 4.72, 95% CI: 3.18–7.01) and steroid usage (OR = 2.19, 95% CI: 1.57–3.07), while there was no significant association between immunotherapy or hormonal therapy and seroconversion after vaccination. Subgroup analyses showed therapies with anti-CD20 antibody (OR = 11.28, 95% CI: 6.40–19.90), B-cell lymphoma 2 inhibitor (OR = 5.76, 95% CI: 3.64–9.10), and Bruton tyrosine kinase inhibitor (OR = 6.86, 95% CI: 4.23–11.15) were significantly correlated with the risk of negative humoral response to vaccination. In conclusion, our results demonstrated that specific oncologic therapies may significantly affect serological response to COVID-19 vaccines in patients with cancer. Thus, an adapted vaccination strategy taking the influence of active treatment into account is in need, and further research on the effect of the third dose of vaccine and the role of postvaccination cellular response in oncologic patients is also needed.

KEYWORDS

cancer, COVID-19 vaccines, serological response, treatment

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 2019 (COVID-19), has led to a global pandemic, causing over 501 million confirmed cases and 6.1 million deaths as of April 2022.¹ Patients with cancer have a very high COVID-19-related morbidity and fatality rate,^{2,3} and optimal therapeutic strategies for this fragile population have not yet achieved.^{4,5} Therefore, the introduction of COVID-19 vaccines is of profound clinical significance in patients with cancer.

Safety and efficacy of vaccines developed against COVID-19 have been well established among the general population,^{6,7} but evidence about their performance is limited among patients with cancer because of their ineligibility in most clinical trials.⁸ Accumulating data suggested that oncological patients, especially patients with hematologic malignancies have an impaired immune response to COVID-19 vaccination compared with healthy controls.^{9–11} Furthermore, anticancer treatments with various therapeutic mechanisms have been reported to impact on response to vaccines. Indeed, patients treated with anti-CD20 monoclonal antibodies developed an attenuated response to influenza and COVID-19 vaccines.^{12–14} Likewise, blunted antibody (Ab) responses were found in patients receiving treatments with Bruton tyrosine kinase inhibitors (BTKi) or B-cell lymphoma 2 inhibitors (BCL2i) at the time of COVID-19 vaccination.^{15,16} As for patients with solid cancer undergoing active treatment, chemotherapy alone or combined with immunotherapy was found to significantly correlate with reduced humoral response after COVID-19 vaccination.^{17,18} Despite the increasing immunogenicity data on oncologic patients, the impact of the broad spectrum of anticancer therapies on serological responses followed by COVID-19 vaccination has not been fully established yet. To narrow this key knowledge gap, we performed a systematic review and meta-analysis to assess seronegative risk among oncological patients on a variety of anticancer treatments compared with patients without active therapy.

2 | METHODS

2.1 | Search strategy and selection criteria

The preferred reporting items for systematic reviews and meta-analyses guidelines were followed in the present study¹⁹ and the study protocol was registered with the PROSPERO international database (CRD42022321660). A literature search from December 1, 2019, to April 1, 2022, was conducted in PubMed, Embase, and Cochrane Library without language restriction. The search term included keywords relevant to COVID-19 (“coronavirus disease 2019” OR “covid-19” OR “2019-nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-CoV-2”) AND vaccine in combination with words related to cancer (“cancer” OR “malignancy” OR “tumor” OR “neoplasm” OR ‘oncology’). The references of included studies were scrutinized and hand-searched for additional eligible studies.

Eligible studies were required to meet the following criteria: (1) clinical study evaluated anti-S immunoglobulin G (IgG) in oncological patients receiving anticancer treatment compared with patients not on treatment at the time of vaccination; (2) original articles reported independent data; and (3) reported relative risks with 95% confidence intervals (CIs) or sufficient information for effect size calculation. Studies using healthy controls were excluded.

2.2 | Quality assessment and data extraction

To limit the risk of introducing bias, a procedure known as the “Newcastle-Ottawa scale” has been used to assess the quality of included studies (9-point scale).²⁰

As different terms were used, groups as treatment-naïve (watch and wait), not on therapy, no treatment, never treated, active surveillance, clinical surveillance, and no ongoing treatment were all categorized as no active treatment during data extraction. A serological positive response was defined based on cut-off value of commercially available kits or in-house assays detecting anti-Spike (S) protein. Data extraction was carried out by two reviewers independently according to a fixed protocol. The following variables were recorded: authorship, publication year, country, study design, number of patients, age, sex, type of malignancy (i.e., solid or hematological tumor), number of patients with cancer undergoing active treatment, number of untreated patients with cancer, cancer status (remission, stable disease, and progressive disease), anticancer treatment strategy (i.e., chemotherapy, immunotherapy, and targeted therapy), type and number of COVID-19 vaccine doses administered, type of anti-S IgG immunoassay, and cut-off value used to define seronegative, time from the last vaccine dose to the serologic test. Data reports were then compared and inconsistencies were resolved by further discussion among all authors through consensus.

2.3 | Outcomes

The primary outcome was the risk of impaired Ab response (assessed by anti-SARS-CoV-2 spike protein IgG Ab testing) in patients receiving anticancer treatment compared with those without active treatment. The secondary outcome was seronegative rate after partial (first dose) or complete (second dose) COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or targeted therapy.

2.4 | Statistical analysis

The odds ratios (ORs) with corresponding 95% CIs were calculated and pooled using the random-effects method for binary outcomes. The significance of the overall ORs was determined using the Z-test. Cochran's Q test and I^2 index ($\leq 50\%$ as low, 50%–75% as moderate, and $>75\%$ as high) were calculated to explore heterogeneity across

studies.²¹ Subgroup analyses based on vaccine dosage (first dose and second dose), type of tumor (solid tumor and hematologic malignancies), type of anticancer therapy (chemotherapy, immunotherapy, targeted therapy, and hormonal therapy), specific drug (anti-CD20, BTKi, and BCL2i), and cancer status were performed. Begg's test was used to assess potential publication bias. The nonparametric Mann–Whitney *U* independent-samples test was used for continuous variables. Type I error rate was set at 0.05 for two-sided analysis. All statistical analyses were done using the STATA software (version 11.0).

3 | RESULTS

3.1 | Characteristics of the studies

A total of 39 reports involving 11 075 patients with cancer were finally included in the present study (Supporting Information: Figure 1) and most were of high quality with a score of 8–9 (Supporting Information: Table 1). There are 31 studies comprising 6637 patients with hematologic malignancies, and 19 studies containing 4278 patients with solid cancer. Most literature investigated the serological response after the second dose of COVID-19 vaccine (including BNT162b2 and messenger RNA [mRNA]-1273). The main characteristics of included studies were summarized in Supporting Information: Table 1.

3.2 | Seronegative risk for patients with active anticancer treatment

Overall, the pooled analysis suggested the risk of serological negative response in patients undergoing anticancer treatment was significantly increased compared to those without active treatment (OR = 2.55, 95% CI: 2.04–3.18, $p < 10^{-5}$, $I^2 = 57.2\%$; Figure 1). In the subgroup analysis, patients with hematologic malignancies on active therapies, were at higher risk of negative response (OR = 3.62, 95% CI: 2.65–4.94, $p < 10^{-5}$, $I^2 = 54.3\%$), than patients with solid cancer (OR = 2.12, 95% CI: 1.52–2.96, $p < 10^{-4}$, $I^2 = 26.2\%$). There was moderate heterogeneity in the overall analysis (Table 1). The seronegative rate after vaccination was significantly higher in patients with active treatment (Figure 2). The analyses based on chemotherapy and targeted therapy obtained similar outcomes after partial or complete vaccination, with a trend toward a lower seronegative rate after the second dose. Sensitivity analysis indicated that no single study influenced the pooled OR qualitatively, and the funnel-plot analysis showed no publication bias ($p = 0.44$, Supporting Information: Figure 2).

3.3 | Seronegative risk for patients with chemotherapy

There are 21 studies investigating the vaccine immunogenicity in patients with cancer undergoing chemotherapy. Poorer response to

COVID-19 vaccine was observed in oncologic patients with chemotherapy compared to those without active treatment (OR = 3.04, 95% CI: 2.28–4.05, $p < 10^{-5}$, $I^2 = 20.4\%$; Supporting Information: Figure 3). When stratified by hematologic malignancies and solid tumor, significant associations persisted (hematologic malignancies: OR = 3.32, 95% CI: 1.30–8.46, $p = 0.012$, $I^2 = 63.1\%$; solid tumor: OR = 2.99, 95% CI: 2.16–4.14, $p < 10^{-5}$, $I^2 = 0\%$).

3.4 | Seronegative risk for patients with immunotherapy

The serologic response among oncologic patients with immunotherapy which mainly included chimeric antigen receptor T-cell therapy and immune checkpoint inhibitors (ICIs), was not significantly lower than those without ongoing treatment in the combined analysis (OR = 1.23, 95% CI: 0.85–1.76, $p = 0.27$, $I^2 = 0\%$; Supporting Information: Figure 4). In the subgroup analysis, we detected a marginal association for patients with solid tumor (OR = 1.71, 95% CI: 1.03–2.84, $p = 0.039$, $I^2 = 0\%$). An additional analysis for therapy with ICIs demonstrated that there is no significant risk of negative Ab response in patients on ICI treatment (OR = 0.71, 95% CI: 0.40–1.25, $p = 0.24$, $I^2 = 38.9\%$).

3.5 | Seronegative risk for patients with targeted therapy

Overall, targeted therapy was significantly associated with increased risk of negative serological response (OR = 4.72, 95% CI: 3.18–7.01, $p < 10^{-5}$, $I^2 = 56.1\%$; Supporting Information: Figure 5) without substantial heterogeneity after analyzing 26 datasets. Patients with solid tumors (OR = 2.87, 95% CI: 1.36–6.08, $p = 0.006$, $I^2 = 43.6\%$) and hematologic malignancies (OR = 6.78, 95% CI: 4.44–10.36, $p < 10^{-5}$, $I^2 = 39.1\%$) undergoing targeted therapy both exhibited an attenuated seroconversion compared with those with no treatments. There were 17 studies assessing the influence of anti-CD20 therapy on the humoral response after administration of COVID-19 vaccine. The result indicated that patients treated with anti-CD20 antibodies had significantly less seropositive responses than those without active therapy (OR = 11.28, 95% CI: 6.40–19.90, $p < 10^{-5}$, $I^2 = 78.9\%$; Supporting Information: Figure 6). In addition, patients treated with BCL2i (OR = 5.76, 95% CI: 3.64–9.10, $p < 10^{-5}$, $I^2 = 0\%$; Supporting Information: Figure 7) or BTKi (OR = 6.86, 95% CI: 4.23–11.15, $p < 10^{-5}$, $I^2 = 42.9\%$; Supporting Information: Figure 8) also had significantly increased risk for seronegative response following COVID-19 vaccination.

3.6 | Seronegative risk for patients with other therapies

There are 10 pieces of literature investigating the effect of steroid therapy on seroconversion after COVID-19 vaccination. Of those, six

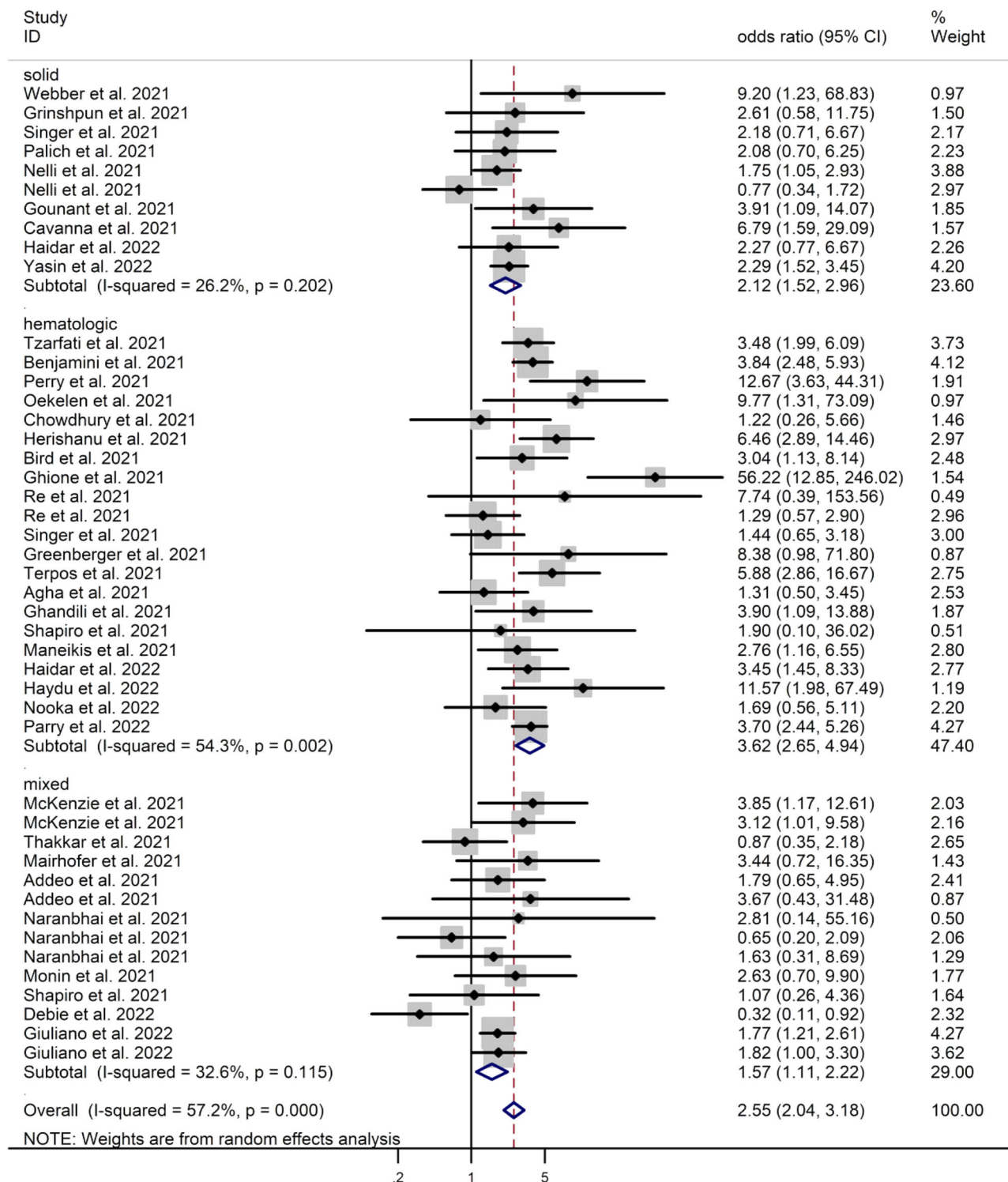


FIGURE 1 Forest plots for the pooled analysis of seronegative risk in patients with anticancer treatments versus patients without active treatments after COVID-19 vaccination. CI, confidence interval; COVID-19, coronavirus disease 2019.

studies assessed the response in patients with hematologic malignancies, while six studies contained patients with solid cancer. Our results indicated a statistically significant association between steroid use and negative Ab response in patients with cancer (OR = 2.19, 95% CI: 1.57–3.07, $p < 10^{-4}$, $I^2 = 39.8%$; Supporting Information:

Figure 9) without significant heterogeneity. Further subgroup analyses by cancer categories yielded similar results (hematologic cancer: OR = 1.67, 95% CI: 1.08–2.60, $p = 0.022$, $I^2 = 19.6%$; solid cancer: OR = 2.91, 95% CI: 1.93–4.40, $p < 10^{-5}$, $I^2 = 32.5%$). We also found a significant relationship between the use of

TABLE 1 Overall and stratified analyses of seronegative risk in oncological patients with anticancer treatment after COVID-19 vaccination

Overall and subgroup analysis	Number of datasets	OR (95% CI)	<i>p</i> (Z)	<i>p</i> (Q)	<i>I</i> ² (%)
Active Treatment	45	2.55 (2.04–3.18)	<10 ⁻⁵	<10 ⁻⁴	57.2
First dose	12	2.05 (1.63–2.57)	<10 ⁻⁵	0.54	0
Second dose	32	2.71 (2.02–3.65)	<10 ⁻⁵	<10 ⁻⁴	65.0
Active Treatment (ST)	10	2.12 (1.52–2.96)	<10 ⁻⁴	0.20	26.2
Active Treatment (HM)	21	3.62 (2.65–4.94)	<10 ⁻⁵	0.002	54.3
Active Treatment (mixed)	14	1.57 (1.11–2.22)	0.011	0.11	32.6
Chemotherapy	27	3.04 (2.28–4.05)	<10 ⁻⁵	0.17	20.4
Chemotherapy (ST)	9	2.99 (2.16–4.14)	<10 ⁻⁵	0.67	0
Chemotherapy (HM)	9	3.32 (1.30–8.46)	0.012	0.006	63.1
Chemotherapy (mixed)	9	2.31 (1.55–3.44)	<10 ⁻⁴	0.94	0
Immunotherapy	18	1.23 (0.85–1.76)	0.27	0.67	0
Immunotherapy (ST)	8	1.71 (1.03–2.84)	0.039	0.72	0
Immunotherapy (HM)	2	1.30 (0.38–4.50)	0.67	0.66	0
Immunotherapy (mixed)	9	0.79 (0.44–1.40)	0.41	0.63	0
Targeted therapy	26	4.72 (3.18–7.01)	<10 ⁻⁵	<10 ⁻⁴	56.1
Targeted therapy (ST)	6	2.87 (1.36–6.08)	0.006	0.11	43.6
Targeted therapy (HM)	13	6.78 (4.44–10.36)	<10 ⁻⁵	0.073	39.1
Targeted therapy (mixed)	8	2.58 (1.16–5.72)	0.02	0.25	23
Hormonal therapy	8	1.16 (0.72–1.86)	0.54	0.38	5.7
Steroid usage	14	2.19 (1.57–3.07)	<10 ⁻⁴	0.056	39.8
Steroid usage (ST)	8	2.91 (1.93–4.40)	<10 ⁻⁵	0.17	32.5
Steroid usage (HM)	6	1.67 (1.08–2.60)	0.022	0.28	19.6
Anti-CD20 therapy	19	11.28 (6.40–19.90)	<10 ⁻⁵	<10 ⁻⁵	78.9
BCL2i	8	5.76 (3.64–9.10)	<10 ⁻⁵	0.91	0
BTKi	14	6.86 (4.23–11.15)	<10 ⁻⁵	0.045	42.9
Immune checkpoint inhibitor	10	0.71 (0.40–1.25)	0.24	0.098	38.9
Immunomodulatory drug	9	2.29 (1.12–4.67)	0.023	0.17	31.3
Metastatic status (metastatic vs. early)	8	0.89 (0.57–1.37)	0.58	<10 ⁻⁴	78.2
Cancer status (stable or progressive disease vs. remission)	9	2.41 (1.47–3.95)	<10 ⁻⁴	<10 ⁻⁴	74.0

Abbreviations: BCL2, B-cell lymphoma 2; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; COVID-19, coronavirus disease 2019; HM, hematological malignancy; *I*², *I*² index for heterogeneity; OR, odds ratio; *p* (Q), *p*-value by Cochran's Q test; *p* (Z), *p*-value by Z test; ST, solid tumor.

immunomodulatory drugs and postvaccination response in patients with cancer (Table 1).

As for the hormonal therapy mainly used in breast and prostate cancer, pooled analysis of seven studies showed no differences between patients with hormonal therapy and those without active treatment (OR = 1.16, 95% CI: 0.72–1.86, *p* = 0.54, *I*² = 5.7%; Table 1).

3.7 | Seronegative risk regarding cancer status and metastatic status

On the basis of eight studies, the analysis showed a significant association between impaired humoral response and cancer status at the time of vaccination. Patients with stable or progressive disease were at a higher risk of seronegative response (OR = 2.41, 95% CI:

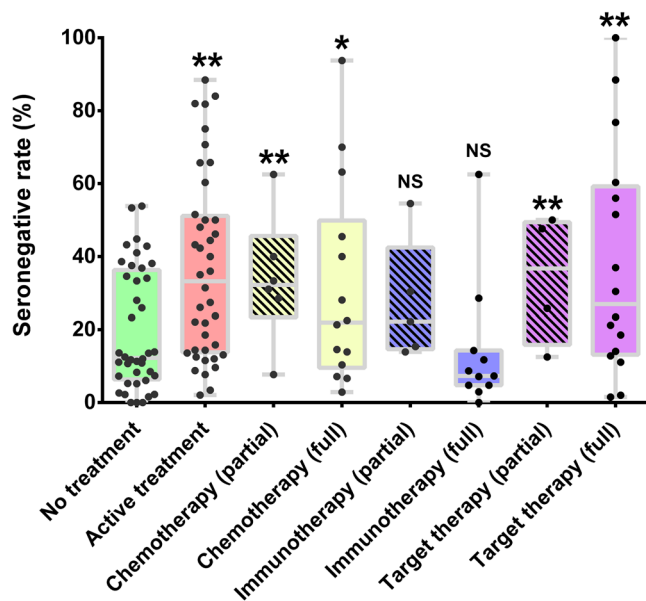


FIGURE 2 Boxplots of seronegative rates (%) in cancer patients treated with different therapy strategies after COVID-19 vaccination. Each point indicates a study cohort where data were available. Pairwise comparisons are based on the nonparametric Mann-Whitney U independent-samples test (patients with no active treatment as a reference group, ** $<10^{-4}$; * $<10^{-3}$; NS, not significant). COVID-19, coronavirus disease 2019.

1.47–3.95, $p < 10^{-4}$, $I^2 = 74.0\%$; Supporting Information: Figure 10) comparing to those at remission stage.

When investigating the possible association between metastatic status and postvaccination response, seven pieces of literature were available for pooled analysis. The result showed metastatic status was not significantly related to the negative response to COVID-19 vaccines (OR = 0.89, 95% CI: 0.57–1.37, $p = 0.58$, $I^2 = 78.2\%$; Supporting Information: Figure 11).

4 | DISCUSSION

Large studies have already reported that patients with solid cancers and hematologic malignancies are at a higher risk of COVID-19 infection, and have an increased rate of disease severity and mortality. The vaccination against SARS-CoV-2 for oncologic patients seems overall safe and immunogenic after well-conducted vaccination schemes. Emerging results showed that adverse events after the first and second vaccine dose in patients with cancer were similar to those observed in the immunocompetent population.²² In addition, there is evidence indicating that the rate of adverse events in actively treated patients was not significantly different from that in patients without active treatment.¹⁶ However, the seroconversion rate in patients with cancer remains lower, delayed, or both compared to the healthy population which may be partially affected by specific anticancer treatments.²³ We performed a comprehensive meta-analysis assessing the impact of anticancer therapies on serological

response to COVID-19 vaccination, and our findings indicated that patients with cancer undergoing treatment are at significantly elevated risk of seronegative response than patients without active treatments. Among patients on therapy, individuals with hematologic malignancies exhibited lower seroconversion compared with those with solid tumors following COVID-19 vaccination, which is in line with prior studies.⁹ Previous evidence indicated that patients with hematologic malignancies were prone to have a poor response to vaccinations, such as vaccines against influenza, herpes zoster, hepatitis B, or pneumococcal infection.^{24–26} And being treated with anti-CD20 antibodies, BCL2i or BTKi might make this situation even worse.^{27,28} In the present study, our results further confirmed the negative influence of therapies with anti-CD20 antibodies (e.g., rituximab), BTKi, and BCL2 inhibitors on serological responses to COVID-19 vaccines in patients with cancer.

Anti-CD20 monoclonal antibodies act by depleting B-cells causing an overall 25% reduction in total lymphocyte count which may be the major reason for decreasing the efficacy of vaccines. Our result suggested that patients with hematologic malignancies, especially those receiving anti-CD20 therapy were most likely to attain negative seroconversion after COVID-19 vaccination, consistent with previous observations.²⁹ Furthermore, it also agrees with the finding that the recovery of memory B-cell pool was delayed compared with normal B-cell ontogeny, which remained below normal controls at 12 months after the last anti-CD20 treatment.³⁰ Besides humoral immunity, COVID-19 vaccination also induces a cellular immune response. In regard to T-cell response after COVID-19 vaccination, activated specific CD4+ or CD8+ response without an IgG response was detected in patients with hematologic cancer on anti-CD20 treatment.³¹ However, there were also other investigations reporting accordantly blunted humoral and cellular responses to COVID-19 vaccines in oncologic patients, while anti-CD20 therapy was significantly associated with seronegative rates but not the lack of T-cell response.³² Moreover, the extent of protection against SARS-CoV-2 by vaccine-induced T-cell response was still unclear.

It has been shown that exposure to SARS-CoV-2 can induce a cellular immune response without seroconversion, and T-cell responses are associated with disease severity and survival of COVID-19.³³ Animal study demonstrated that cellular immune response contributed to protection against SARS-CoV-2 when Ab response was insufficient in *Rhesus macaques*.³⁴ A recent study indicated that there were robust T-cell responses recognizing the new Delta and Omicron variants in patients with multiple sclerosis on anti-CD20 treatment after receiving COVID-19 vaccines.³⁵ In addition, this study also illustrated that the third dose of vaccination significantly increased the frequency of CD8+ T-cells, which are of particular importance in viral clearance. Similarly, the study by Re et al.³⁶ evaluated both B- and T-cell responses in patients with lymphoid malignancies after the third dose of the COVID-19 vaccine and found an emerging cellular response in several patients who were seronegative after completing two doses of vaccination. Of note, most of these seronegative patients had received anti-CD20 treatment. All these findings suggested that cellular immunity may

play an important role in protection against SARS-CoV-2, and patients taking B-cell depleting therapy may still benefit from COVID-19 vaccination. Further studies are required to define the exact role of the T-cell response following vaccination and the possible effect of a third dose of the vaccine, particularly in patients receiving anticancer therapies, such as anti-CD20.

BTKi and BCL2i are novel biological agents widely used in the treatment of chronic lymphocytic leukemia (CLL). BTKi acts by disrupting of the B-cell receptor signaling pathway, which may suppress Ab immune response. Previous evidence illustrated that BTKi therapy impaired humoral response to influenza and hepatitis vaccines among CLL patients.^{27,37} A recent study evaluated the humoral and cellular response of the recombinant zoster vaccine in CLL patients, which indicated that both immune responses were attenuated in those on BTKi therapy compared with treatment naïve patients.³⁸ BCL2i, like venetoclax, was found to be associated with decreased seroconversion rate, while the response rates were lower when combined with anti-CD20 antibodies.²² In CLL patients with venetoclax monotherapy, some developed a positive response but with low Ab titers.¹⁶ Although our results contributed to a better understanding of the effect of these two treatments on the humoral response to the COVID-19 vaccine in patients with cancer, more data are needed for verification.

Our results showed that oncologic patients treated with cytotoxic chemotherapy developed an impaired immune response following vaccination against COVID-19. It has been suggested that chemotherapy was significantly associated with a negative or weak response after the first vaccine dose among patients with solid tumors.^{10,39,40} Although the anti-S IgG titer level may improve after the second vaccination,³⁹ existing pieces of literature indicated that chemotherapy was correlated with a poorer seroconversion rate in patients with solid tumors and hematologic cancer compared with those without active treatment after the second vaccine dose, which supported our conclusion.^{41–43} Several investigations demonstrated that patients with chemotherapy plus immunotherapy or steroid treatment had a significantly lower response after COVID-19 vaccination.^{15,44} Results from the present study indicated that steroid usage alone contributed to a significantly higher risk of negative seroconversion in patients with cancer, but immunotherapy did not. Thus, a third dose of vaccination and routine serological monitoring after vaccination in patients with cancer on chemotherapy and with steroid use may be needed.

We found no correlation between hormonal or ICI therapies and blunted serological response following COVID-19 vaccination. Accumulating evidence showed oncologic patients with hormonal therapy had high seroconversion rates and excellent Ab titer levels comparable with those receiving no treatment which supported our result.⁴⁰ Although ICI can stimulate immune system function, the incidence of adverse events after COVID-19 vaccination in oncologic patients receiving ICI therapy seemed similar with that of healthy individuals.⁴⁵ Previous evidence about the potential impact of ICI on the humoral response to COVID-19 vaccines has been inconsistent. Our pooled analysis provided new information to clarify this discrepancy, while further research may be warranted.

The immune response after administration of COVID-19 vaccines may be affected by multiple factors, such as cancer, HIV, autoimmune conditions, transplants, and medications/treatments received.⁴⁶ Moreover, it has been shown that post-COVID-19 fungal infections may target the immunocompromised population, which might also interfere with the body's inner immunity.⁴⁷ Compared with other hematologic malignancies, the Ab response to vaccination appears particularly impaired in CLL patients with seroconversion rates of 40%–60%, while ongoing CLL-directed therapies and disease status further affected the response.^{16,48,49} Our study supported these earlier findings and identified a significant association between anti-CD20, BTKi, or BCL2i treatments and reduced humoral responses in patients with hematologic malignancies compared to patients without active therapy. Furthermore, we found a significant correlation between cancer status and postvaccination response, which may be explained by the dynamic change of the autoimmune system in the cancer progression. Prior study has shown that as the stage and grade of tumor advances, CD4/CD8 ratio and CD30 expression levels are increased which might exert an influence on the immune response after vaccination.⁵⁰

There are several limitations in the current study. First, the literature included was heterogeneous in terms of cancer type, vaccine type, treatment categories, and the interval between treatment and vaccination. Due to the relatively small sample size of specific cancer subtypes, a broad range of cancers stratified as solid tumor and hematological malignancy were analyzed, which did not allow us to perform more refined analyses. As for vaccine type, included studies were dominated by mRNA vaccines, and data regarding inactive SARS-CoV-2 vaccine or recombinant adenovirus vaccine are currently limited. However, there was no significant difference in seropositivity rates between BNT162b2 and non-BNT162b2 (including mRNA-1273, AZD1222, and Ad26.COV2.S) reported in most studies. Second, the time point and serological assays of immune response assessment were different across studies. Different commercial kits may differ in sensitivity, however, previous studies indicated that different kits show acceptable performance and are consistent in results.⁵¹ Third, since included studies involve a wide spectrum of cancer, study protocols (e.g., Ab detecting assay, sampling time), vaccine platforms, treatment strategies, and duration of active treatment, further analysis adjusted by these covariants should be conducted if all individual raw data were available.

In summary, our study suggested that oncologic patients undergoing anticancer treatment were at a higher risk of suboptimal humoral response after both partial and complete vaccination against COVID-19, specifically in those with chemotherapy, targeted therapy, and steroid usage, compared to patients without active treatment at the time of vaccination. Therefore, the period without active treatment seems an optimal time window for patients with cancer to get an immunization, and an adapted vaccination strategy, such as a third dose, heterologous vaccine regimens, and temporary adjustment of anticancer therapy, may be required. In addition, the effect of postvaccination cellular response and long-term efficacy of vaccination require detailed study and updates for this vulnerable population in the coming future.

AUTHOR CONTRIBUTIONS

Concept and design: Kefu Tang and Xi Wu. *Acquisition and interpretation of data:* Kefu Tang, Zhiying Wei, and Xi Wu. *Drafting of the manuscript:* Kefu Tang and Xi Wu. *Critical revision of the manuscript:* Kefu Tang and Xi Wu. *Final approval:* All authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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