

COVID-19 vaccination efficacy and safety in individuals with solid tumors or hematologic malignancies

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Abstract. Cancer patients are immunocompromised, and inadequate antibody response after the SARS-CoV-2 vaccine (SC2V), which puts them at increasing risk of Covid-19 severe disease. Moreover, the data on adverse reactions in those patients is fragmented and lacking after the SC2V. The objective of this study was to evaluate the immunogenicity and effectiveness as well as safety of the SC2V in those patients. The data for this study was obtained from the Pubmed database, as of August 23, 2023. A total of 614 documents were collected. The period of first, second, third and fourth doses of the SC2V are labeled as T1, T2, T3 and T4, respectively. The serologic conversion rate of the patients following vaccination served as a measure to evaluate the vaccine's immunogenicity. As a result, 17 researchers altogether were included. The effect size (ES) for serological conversion rate of solid tumors (STs) were 0.51 (95% CI: 0.40-0.67), and 0.88 (95% CI: 0.85-0.92) respectively, after T1 and T2. The ES for serological conversion rate of hematologic malignancies (HMs) were 0.08(95%CI:0.00-1.61), 0.60(95%CI:0.44-0.82, 0.84(95%CI:0.77-0.93), respectively, after T1, T2, and T3. Comparing the serologic conversion rate between T2 and T3 for STs as well as HMs, it revealed poor outcomes for HMs, which may be related to different types of cancer and treatment regimens. In all studies, local discomfort was the most frequent adverse response. The chemotherapy group had the greatest influence on the SARS-CoV-2 vaccine immunogenicity, compared to other treatments. In conclusion, SC2V is safe and effective for cancer patients.

Keywords: SARS-CoV-2 vaccine; cancer; seroconversion rate; safety; COVID-19.

1. Introduction

The novel coronavirus outbreak of 2019 caught the world by surprise and caused huge losses to the global economy. As of August 8, 2023, more than 6.95 million fatalities and over 760 million COVID-19 infections have been verified globally (<https://covid19.who.int/>). Although the mortality rate had almost halved [1] compared to December 31, 2021, the relatively high transmission rate and the constant mutation of the virus made the SARS-CoV-2 vaccine an immediate need to address the outbreak. Especially for immunocompromised people, current research shows that patients with cancer, organ transplantation, HIV infection, end-stage renal disease, etc. are at high risk of infection and severe pneumonia [2].

Currently, live attenuated, inactivated, protein subunit, viral vector (VV), RNA, DNA, and virus-like particle (VLP) vaccines are the most common forms of SC2V. Viral vector vaccines, protein subunit vaccines, and mRNA vaccines are able to generate further cellular or humoral immune regulation, including Th-cell responses and germinal center responses, and also the creation of associated memory cells, considerably enhancing their effectiveness. Although some VVs or mRNA vaccinations may cause adverse reactions including thrombocytopenia and myocarditis [3]. These reports have raised public concerns about the SARS-CoV-2 vaccine (SC2V) s' safety.

This review aims to address cancer patients' worrisome and evaluate the efficacy as well as SC2Vs' safety in such immunocompromised patients, using the seropositivity rate as an indicator of those hematologic malignancies (HMs) or solid tumors (STs) patients.

2. Methods

Until August 23, 2023, only Pubmed database had been used to search relevant studies, including 3-year studies from 2021 to 2023 with no language restriction.

2.1. Search strategy

The query terms were included as follow Fig. 1, and the relevant literature is shown as Fig. 2.

Type	Query terms
Cancer	TUMOR OR CANCER OR MALIGNANCY OR NEOPLASIA OR LEUKEMIA OR LYMPHOMA OR SARCOMA OR NEOPLASM OR MYELOMA
Virus	COVID-19 OR SARS-COV-2
Vaccination	VACCINE OR BNT162B2 OR AZD1222 OR MRNA1273 OR SINO VAC OR SINOPHARM
Index	ANTIBODIES OR IMMUNORESPONSE OR RESPONSE OR HUMORAL OR SEROCONVERSION OR SEROPOSITIVITY OR IMMUNOGENICITY OR VACCINE
Others	VACCINE SAFETY

Fig 1. Term list.

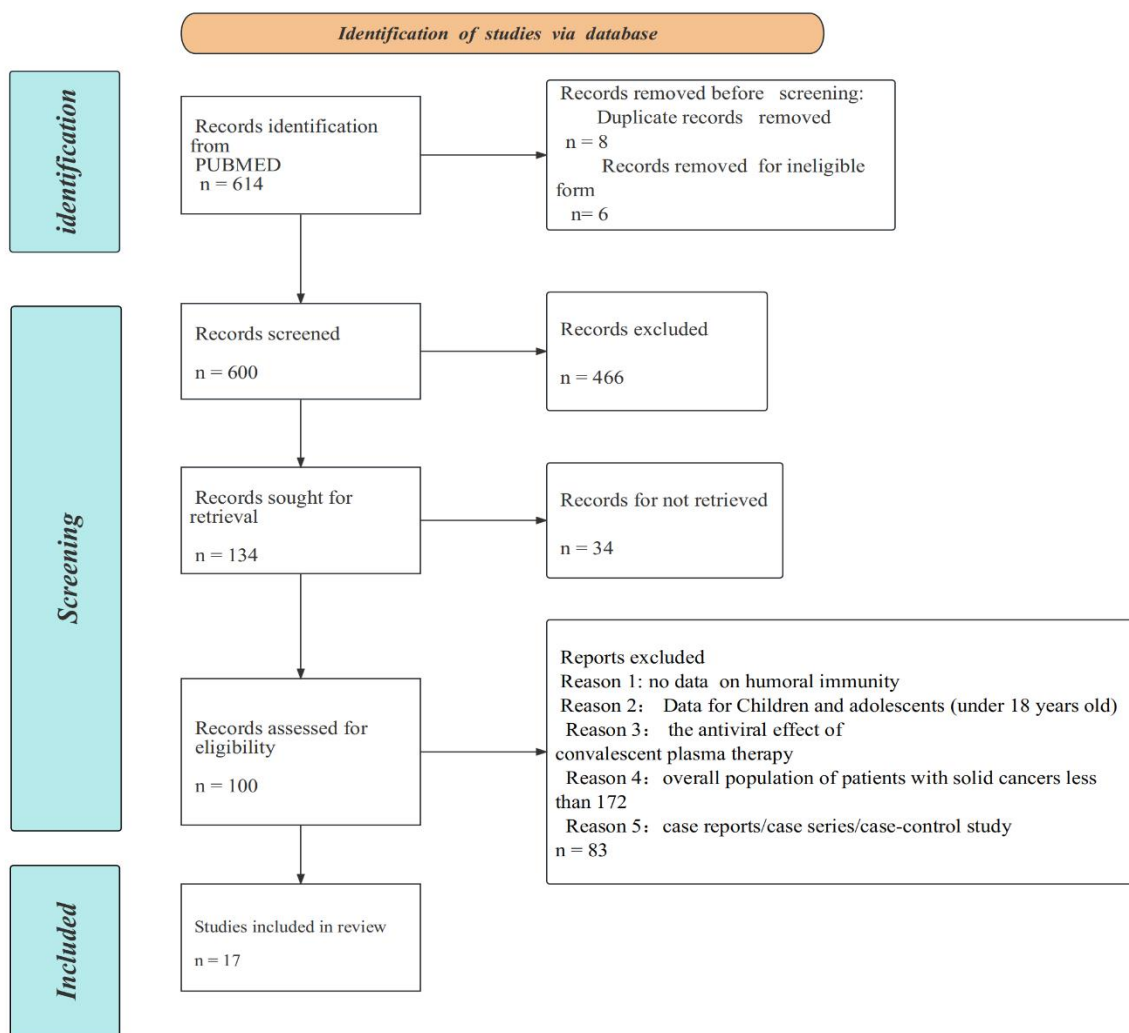


Fig 2. Flow diagram.

2.2. Study selection

The selection parameters for the literature included RCT (randomized clinical trials) or non-randomized clinical design as well as cohort study whose content contained adult patients with HMs or STs were vaccinated against COVID-19. Studies should have reported the serological conversion rate of different groups of people and studies only adults over age of 18 should be included. Using the WHO sample size criteria, the minimal sample size for estimating SC2V efficacy is determined to be 172. So less than 172 patients in total had been excluded from each study's population. Case reports were excluded.

2.3. Measures of outcome

The main outcome was the humoral response after immunization, measured by IgG level (IgG levels above 50 AU/ml were considered as seropositive). Other outcome indicators included, after various cancer treatments, the vaccine's effectiveness and safety.

2.4. Statistical analysis

Review Manager 5.3 was used to compare the serological conversion rates of patients with solid cancers and hematological cancers compared to the healthy population after COVID-19 vaccination respectively, and STATA 12.0 was used to simplify the differences in serological conversion rates between patients with solid tumors (STs) and hematological cancers. Risk ratios (RR) and the random effects model were used to evaluate statistical heterogeneity and dichotomous variables, respectively. All results were presented with 95% confidence intervals (CIs).

3. Results

This study investigates the efficacy of SC2V in patients following vaccination with various vaccine doses and the serologic conversion rates of patients following various treatment regimens. The vaccine safety in cancer patients is explored through the occurrence of adverse reactions.

3.1. Efficacy (hematological response) of the SC2V in solid tumors and hematologic malignancies

The systematic study of the literature included 614 relevant studies. After checking for duplicates as well as deleting non-compliant documents such as letters, a total of 600 documents were obtained. After a rigorous screening and evaluation process, 17 documents that met the above criteria were finally selected (Figure 1). For vaccine efficacy, STs versus healthy populations accounted for 9 articles with a total of 3,397 patients, hematological cancers versus healthy populations accounted for 3 articles with a total of 654 patients, and STs versus hematological cancers accounted for 5 articles with a total of 1,235 patients. Since vaccines approved by the World Health Organization have all achieved 50% or higher efficacy. Heterogeneity among the different SARS-CoV-2 vaccines was not considered significant in this paper. Therefore no subgroup analysis of vaccine types was performed.

3.1.1. Solid cancers/Hematologic malignancies vs. Healthy population

For STs, four studies reported data on serological conversion rates after T1, with 73.99% in healthy populations and 39.66% in STs. ES was lower for STs Patients (RR: 0.51[95%CI: 0.40-0.67]). Eight studies reported data on serologic conversion rates after T2, including 97.42% in healthy populations and 85.71% in STs. ES was lower for the same population (RR: 0.88[95%CI: 0.85-0.92]) (Fig. 3). Despite the poor antibody production by STs to the SC2V, the serological conversion rate increased significantly after the second vaccination. However, data on seroconversion were gathered after immunization at different intervals.

For HMs, three studies reported data on serologic conversion rates after T1, with 93.85% in healthy populations and 10.58% in patients with HMs. ES was lower for hematological malignancy patients (RR:0.08[95%CI:0.00-1.61]). Two studies reported data on serologic conversion rates after T2 which

was 68.18% in the healthy population and 43.75% in patients with HMs. ES was lower for hematological malignancy patients (RR:0.60[95%CI:0.44-0.82]). Data on serologic conversion rates of SC2V after T3 were published in research., in which the serologic conversion rate was 100% in the healthy population and 83.70% in patients with HMs. ES was lower for hematological malignancy patients (RR: 0.84[95%CI: 0.77-0.93]), serologic conversion rates significantly increased after the third dose of the SC2V in hematologic malignancy patients (Fig. 3). Similarly, data on seroconversion was gathered after immunization at various non-constant times.

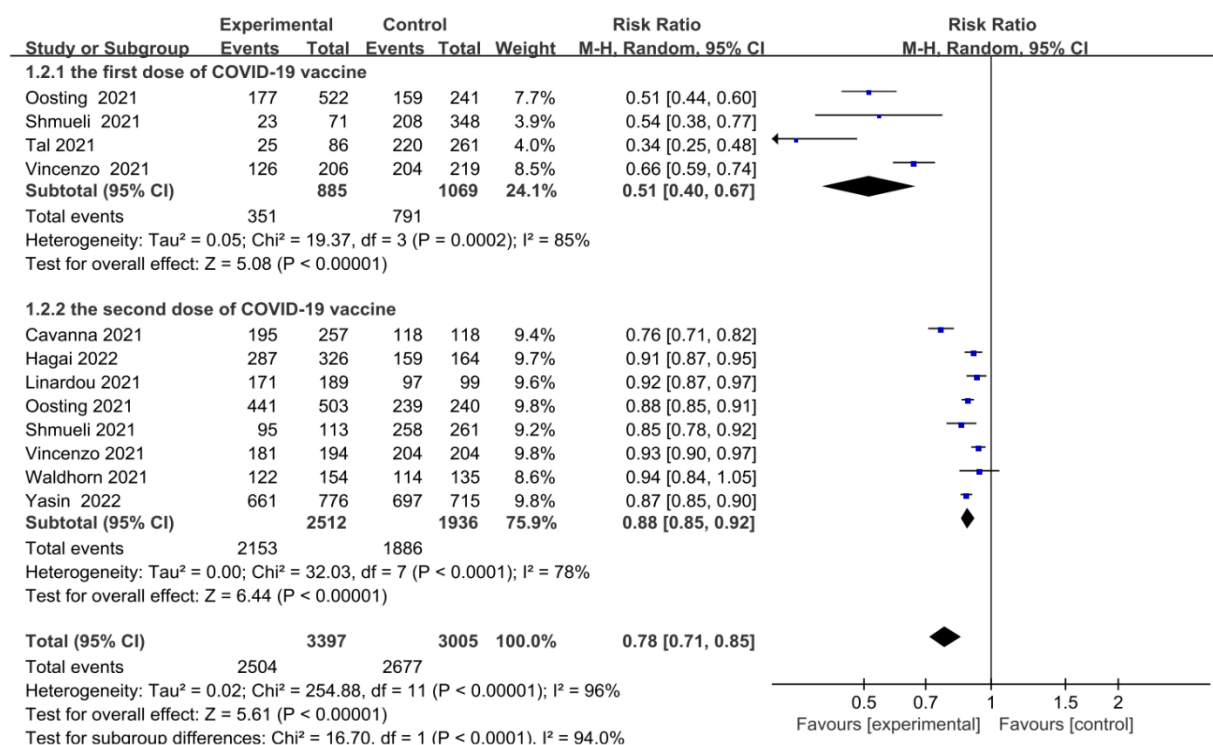


Fig 3. ES between STs and healthy population [4-12].

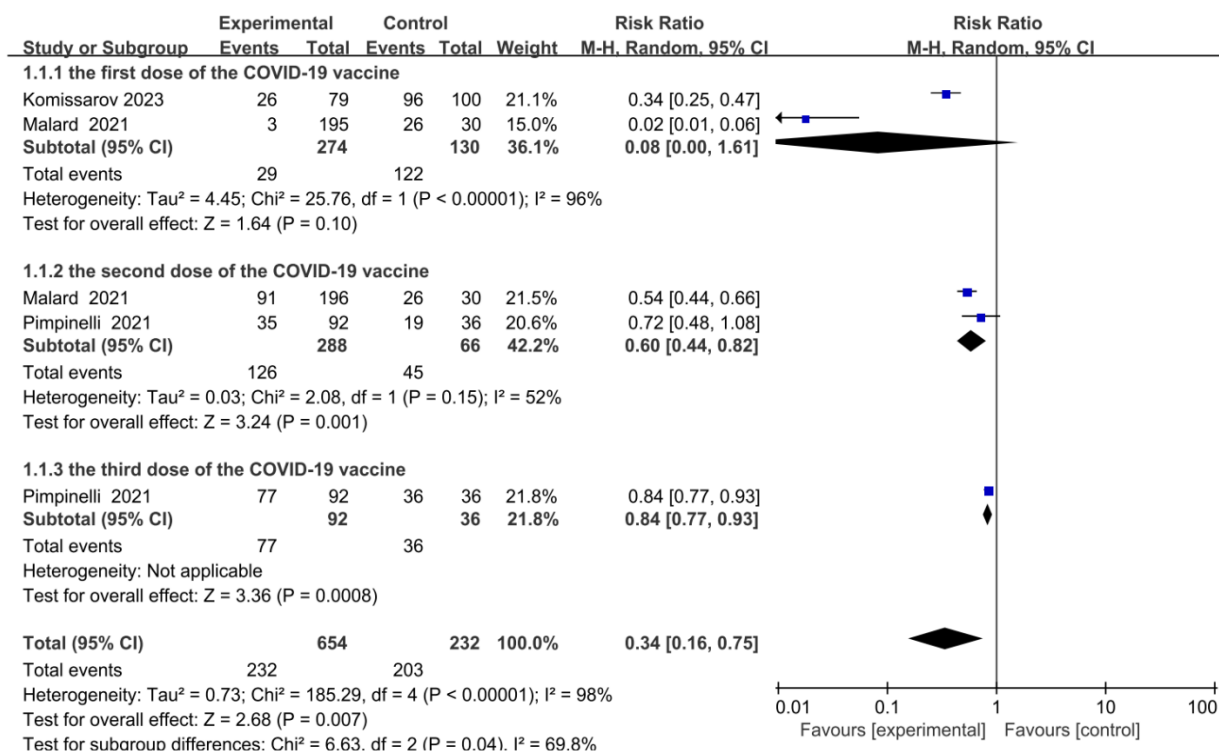


Fig 4. ES between HMs and healthy population [13-15].

3.1.2. STs vs. HMs

Figs. 3 and 4 show that patients with hematologic cancers did not have the same rate of immune response as those with STs after receiving the SC2V. Studies including only two or more doses of the vaccination were chosen in order to test this hypothesis, taking into account the unsatisfactory immune response of all tumor patients following T1. Five relevant papers were collected and categorized into subgroup 1 (two doses of the SC2V), and subgroup 2 (three doses of the SC2V), including 1235 patients with STs and 710 patients with HMs which showed an immune response rate of 86.56% in solid cancer group and 65.77% in hematological malignancies group (Fig. 5). ES were higher for patients with STs (RR: 1.43[95%CI: 1.16, 1.76]) (Fig. 6), which suggested that compared to STs, hematologic malignancy patients have a worse immune response to SC2V, so they require more attention.

	study	Solid cancer			Hematologic malignancies		
		seropositivi	seronegativ	total	seropositivi	seronegativ	total
two dose of vaccine	Fendler 202	380	67	447	81	57	138
	Mona 2021	226	28	254	13	8	21
	Paolo 2021	110	4	114	53	48	101
	Anna 2023	114	13	127	118	39	157
	Annika 202	66	50	116	32	52	84
three dose of vaccine	Anna 2023	126	1	127	142	15	157
	Annika 202	47	3	50	28	24	52

Fig. 5 Solid cancer vs HMs after two and three dose of vaccine [16-20]

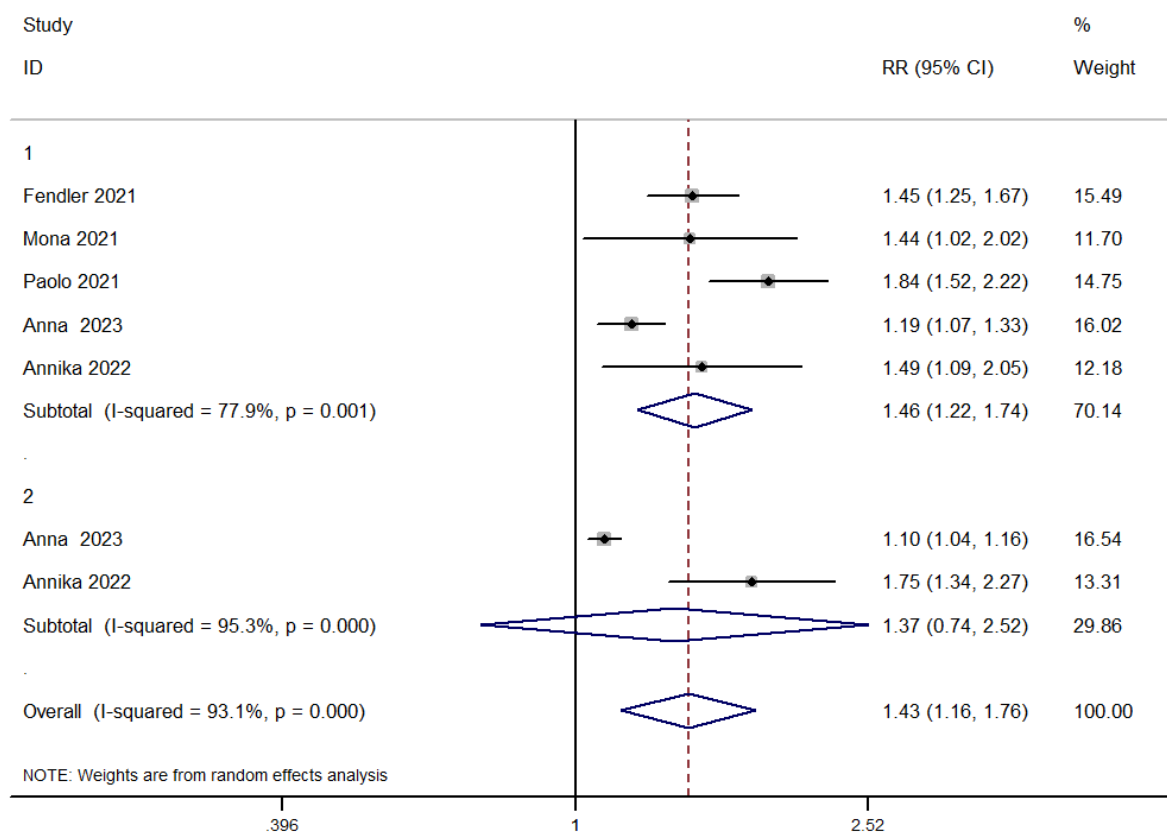


Fig. 6 ES between STs and HMs [16-20]

3.2. SC2V immunogenicity after different types of treatment and evaluation of the vaccine safety

For those patients, in addition to the underlying malignancy itself affecting immunity, different treatments can also cause immunocompromised to some extent. Mechanisms of injury include the

myelosuppressive effects of cytotoxic chemotherapy, adoptive cell transfer therapy effects, etc. Specifically, the immune system can be impaired by corticosteroids, B-cell depletion therapy, cellular therapies, stem cell transplants, etc., thereby affecting the efficiency. In a study by Ayse Irem Yasin et al. [5], patients who received active chemotherapy (n=309), immunotherapy (n=42), targeted therapies (n=178), and those who did not receive all of the above treatments (n=350) were investigated separately. The serologic positive conversion rates after the second dose were 78.6%, 85.7%, 86.0%, and 91.1%, respectively. Another study by Vincenzo Di Noia et al. on the assessment of immunogenicity in cancer patients (n=1090) showed that aggressive chemotherapy and long-term steroid use were strong predictors of a reduced serological response, especially in hematologic malignancy patients or after intense immunosuppressive therapy treatments [9]. It is undoubted that treatments for cancer, such as targeted therapies, can affect the effectiveness of the SC2V, but the impact on the immunogenicity of the SC2V is greater after aggressive chemotherapy.

Similar results were found in comprehensive research by C. Corti et al., which demonstrated that a substantial percentage of patients undergoing systemic cytotoxic treatment for STs had sluggish or non-responding responses to a single dosage of the vaccine [21]. In addition, the immune system can respond to vaccines in cancer patients receiving targeted therapy with receptor tyrosine kinase inhibitors (e.g., erlotinib, sunitinib, and imatinib) or monoclonal antibodies such as trastuzumab. In a large multicenter study by Qi Mei et al, it was noted that the efficacy of monotherapy was not reduced in the group which vaccinated with the SC2V compared to the unvaccinated subgroup, although minor side effects occurred [22]. A study by Dana Raluca Arbore et al indicated that TKI treatment of patients with chronic granulocytic leukemia (CML) was well tolerated and there was no statistically significant relationship between adverse reactions after vaccination and hematological parameters of the patients [23].

For the majority of cancer patients who had received the SC2V, side effects are mild and tolerable, mainly characterized by fever, injection site pain, dizziness, body aches, abdominal pain, myalgia, headache, chills, and shortness of breath, diarrhoea, runny nose, dry throat and fatigue. Localized discomfort was the most frequent adverse effect while allergic reactions were rare. Additionally, compared to T1, the rate of adverse events was higher following T2 [4]. Furthermore, the concurrent use of SC2V and anti-PD-1 agents simultaneously increases co-stimulation and decreases co-inhibitory modulation between antigen-presenting cells and T-cell receptors, which may cause an accumulation of the immune response and be linked to an increase in the frequency of severe irAE (immune-related adverse event) in such patients [22]. To avoid severe adverse reactions, determining the optimal time interval between vaccination of SARS-CoV-2 and anti-PD-1 therapy plays a vital role.

4. Discussion

After T1, cancer patients had much lower levels of antibodies than the general population, according to this study. Seropositive conversions in patients with HMs were still low despite an improvement after the second vaccination dose, suggesting the need for booster shots in these patients, particularly for those receiving B-cell depletion therapy, where the immune response significantly improved after T4[24]. In addition, except the situation of specific critical symptoms, SC2V is proven to be safe and effective in cancer patients. Despite the fact that several viral vectors or mRNA vaccines have been connected to side effects in the healthy population such as thrombocytopenia and myocarditis, the cancer patients in the current investigations had no such adverse effects [25]. Vaccination is recommended for cancer patients in full course, full dose, and in accordance with the recommended dosage and number of doses.

There are, of course, some limitations to this study. On the one hand, the study's confounders, which include particular cancer kinds (e.g., B-cell and other HMs), cancer stages, and disease activity (e.g. current illness or remission), are quite complicated. On the other hand, a variety of anticancer medications (e.g., immune checkpoint inhibitors and B-cell depleting agents) and other potent

treatment modalities that are being employed in clinical practice should be taken into account, which all significantly affects the ability of tumor patients to respond adequately to the SC2V. Moreover, effectiveness and protection also vary among vaccines. In addition, variants of different new coronaviruses, time of vaccination, time of antibody testing, and co-morbidities with other types of diseases in cancer patients should have been taken into consideration. However, they were excluded from the analysis of the study due to insufficient reporting of pertinent information. Various factors made the study highly heterogeneous, further highlighting the complexity of the immune response in this particular population.

Even while some negative side effects brought on by cancer or cancer treatment may be misconstrued for vaccine-related systemic side effects, the current study does not identify any major adverse reactions in cancer patients after receiving the SC2V. To reduce the side effects of post-treatment as well as the difficulties related to cancer patients, it is still imperative to boost first-level prevention.

Moreover, the analysis done in this study on patients with hematologic cancers is relatively small and lacks corresponding data. So, the immunogenicity and safety of different types of hematologic cancers after vaccination with the SC2V need to be further analyzed.

Finally, it is recommended that cancer patients should be given a personalized vaccine plan as well as a strategy to restart antitumor therapy after a comprehensive evaluation of the patient's physical immune function and condition, in order to prevent the development of severe adverse effects.

5. Conclusion

In summary, the SARS-CoV-2 vaccination is both secure and efficient. At the same time, the likelihood that cancer treatment will interfere with the efficacy of the vaccine need to be reduced, especially in the period of aggressive chemotherapy. There is lower vaccine efficacy in hematologic malignancies compared to solid tumors, so booster or update vaccinations should be considered to prevent serious COVID-19 outcomes.

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