Efficacy and safety profile of two-dose SARS-CoV-2 vaccines in cancer patients: An observational study in China

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Abstract

BACKGROUND
The new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has produced a global pandemic of coronavirus disease 2019 (COVID-19), resulting in modifications to public health policies on a universal scale. SARS-CoV-2 vaccine has evolved as the most effective and secure way for protecting healthy individuals against COVID-19. Patients with cancer were excluded from clinical trials due to their increased COVID-19 risk and current immunosuppressing therapy. Safety and effectiveness evidence is insufficient for SARS-CoV-2 vaccination in cancer patients.

AIM
To assess the efficacy and safety of two-dose SARS-CoV-2 vaccines in cancer patients.

METHODS
A multicenter observational study was performed at ten Chinese hospitals between January 1, 2021 and December 31, 2021. Each participant in the research received two doses of vaccination. A total of 215 healthy people were screened and 132 eligible patients with cancer were recruited. In order to verify the safety of the second dose of the vaccine, a side-effect report was compiled. Two weeks following the second vaccination dose, subjects underwent an analogous questionnaire survey. Utilizing a magnetic particle-based chemiluminescence immunoassay, serum levels of anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies were measured to determine the effectiveness of vaccination. IgG
levels ≥ 10 AU/mL were considered seropositive.

RESULTS
All the 347 eligible patients completed the follow-up, and anti-SARS-CoV-2 IgG antibodies were detected. Local pain at the injection location was the most common side effect mentioned by all responders, with an increased incidence in cancer patients than the healthy people after the second dose vaccine (17.2% vs 9.1%; \(P = 0.035\)). There was no significant difference in headache, urticaria, or other adverse reactions between patients with cancer and healthy people. In the group of cancer patients, the seropositivity incidence was 83.3%, while it was 96.3% in the group of healthy people. In the group of cancer patients, the seropositivity incidence and antibody levels were significantly lower \( (P < 0.001) \). This analysis showed a poorer response rate in patients on active immunosuppressive treatment and elderly cancer patients.

CONCLUSION
Two-dose Chinese vaccines are effective and safe in cancer patients. However, further research is required on the efficacy in elderly cancer patients and those on active immunosuppressive treatment.

Key Words: SARS-CoV-2; Vaccine; Cancer; COVID-19; Immunotherapy

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Core Tip: Newer strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have made the ongoing global coronavirus disease 2019 pandemic critical. Patients with cancer form a high-risk group, as those with active cancer or those treated with immunosuppressive therapies are more likely to be infected by SARS-CoV-2. Our study indicated the efficacy and safety of two-dose SARS-CoV-2 vaccines in cancer subjects.

INTRODUCTION
The new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has produced a global pandemic of coronavirus disease 2019 (COVID-19), resulting in modifications to public health policies and causing many patient deaths worldwide[1]. As of April 2, 2022, 47583 cases of COVID-19 have been diagnosed and 13436 patients have been dead in China. SARS-CoV-2 vaccine was considered to be the preventive way of accomplishing sufficient herd immunity against SARS-CoV-2 infection to eventually stop the COVID-19 pandemic. More than 3.2 billion doses of SARS-CoV-2 vaccine have been administered until April 2, 2022 in China, and almost 1.28015 billion Chinese have undergone SARS-CoV-2 vaccination.

Patients with cancer have been recognized as a highly vulnerable group, and it is of important significance to clarify the risk and efficacy of vaccination as patients with active cancer or those treated with immunosuppressing therapies are more likely to be infected by SARS-CoV-2 and develop severe illness if infected[2,3]. Even though, there is a higher mortality in cancer patients than in healthy people [4]. However, it is unknown whether COVID-19 vaccination is effective and safe for cancer patients as almost all vaccine-evaluated clinical trials excluded cancer patients[5]. Current recommendations suggest cancer patients to undergo SARS-CoV-2 vaccination against COVID-19, despite the absence of solid data on the effectiveness and safety of these vaccines in cancer patients[6].

Therefore, we aimed to clarify and compare the efficacy and safety of SARS-CoV-2 vaccines between cancer patients and non-cancer individuals. The findings would improve clinical care, protect these vulnerable patient populations, and help the government to formulate corresponding policies.
MATERIALS AND METHODS

Study design and patients
This is a multicenter observational study performed at ten Chinese hospitals from January 1, 2021 to December 31, 2021. We screened 215 healthy people and 132 eligible patients with cancer were recruited. All healthy people and cancer patients underwent double-dose SARS-CoV-2 vaccination. China has released SARS-CoV-2 inactivated vaccines from the Beijing Institute of Biological Products, Wuhan Institute of Biological Products, and Sinovac. Two weeks after the second vaccination dose, an identical survey was completed online or by telephone to report side effects. Using a magnetic particle-based chemiluminescence immunoassay, serum levels of anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies were measured to determine the efficacy of vaccination. The safety and efficacy in cancer patients after double-dose SARS-CoV-2 vaccination were evaluated. The study was approved by the Clinical Research Ethics Committees of Anhui Medical University Affiliated with Wuxi Clinical College (Approval number: YXLL-2020-003).

The trial was explained to participants, their family members, or legal counsel. The patients’ competency was then evaluated based on their appropriate time allocation, location, and personality, as well as their comprehension of the presentation. All potential participants provided written informed consent.

Assessments
Approximately two weeks after the second vaccination dose, an analogous telephone or online questionnaire was performed. Vaccine recipients were asked if they had experienced any similar signs like: Fatigue, localized soreness, or injection site edema. Additionally, they were allowed to report symptoms not listed in the survey. We also recorded the baseline characteristics of the study population including treatment delivery, data collection, and outcome assessment. Additionally, 5 mL of peripheral venous blood was collected from subjects, centrifuged at 2500 rpm for 10 min, and stored at -80 °C. SARS-CoV-2 specific IgG antibodies were evaluated by the magnetic particle chemiluminescence method. iFlash 3000 (YHLO, China) and IgG antibody detection Kit (YHLO, China) were used to quantify IgG antibody levels following the manufacturer’s instructions. An IgG level ≥ 10 AU/mL was considered seropositive.

Statistical analysis
The differences in continuous variables, expressed as the mean ± SD, between the two groups were tested by the student’s t-test or Mann-Whitney U test. Categorical variables are represented as n (%), and were compared by the chi-squared test or Fisher’s exact test and continuous data by the Wilcoxon rank-sum test. In calculating the mean difference or risk ratios with 95% confidence intervals, P-values < 0.05 were judged as statistical significance. Statistical analyses were performed with SPSS Statistics (v. 20, IBM, Chicago, IL). No interim analysis was included in the assessments. Data overseeing was performed by the 904th Hospital of PLA.

RESULTS

Baseline patient characteristics
A total of 347 subjects underwent assessment between January 1, 2021 and December 31, 2021. Among them, 215 healthy people were screened and 132 eligible patients with cancer were recruited. All 347 eligible subjects completed the follow-up, and anti-SARS-CoV-2 IgG antibodies were detected. Table 1 depicts the demographics and features of the study subjects.

Adverse effects and safety evaluation
Two doses of SARS-CoV-2 vaccines were administered to cancer patients to evaluate their safety. All adverse effects were recorded for the second dose. According to the cancer patient group, total side effects occurred in 28.8% of those who received the second dose of the vaccination, and 34.4% in healthy adults. The incidence of side effects reported after the second dose had no significant difference between the two groups (P = 0.215). The most frequent adverse events were tiredness (15.9%), headache (12.9%), and local pain (9.1%) in the cancer patients, while the first three common adverse were local pain (17.2%), headache (12.1%), and fever (10.7%) in the healthy people. The rate of local pain was significantly higher in the healthy people than in the cancer patients (P = 0.035, Table 2), and the incidence of tiredness was increased significantly in the cancer patients than in the healthy people (P = 0.045, Table 2). The incidence of other adverse effects showed no significant difference between the two groups (P > 0.05, Table 2).

Efficacy evaluation
The identification of SARS-CoV-2 specific IgG antibodies 2 wk after the administration of the second
Table 1 Demographic and baseline characteristics of the study population in the two groups

|                      | Healthy | Cancer | P value |
|----------------------|---------|--------|---------|
| Number               | 215     | 132    | < 0.001 |
| Age                  |         |        |         |
| mean ± SD            | 46.2 ± 8.1 | 58 ± 5.4 |         |
| Sex                  |         |        | 0.12    |
| Male                 | 137 (63.7%) | 73 (55.3%) |         |
| Female               | 78 (36.3%) | 59 (44.7%) |         |
| History of hypertension |       |        | 0.17    |
| Yes                  | 69 (32.1%) | 52 (39.4%) |         |
| No                   | 146 (67.9%) | 80 (60.6%) |         |
| Smoking history      |         |        | 0.06    |
| Yes                  | 50 (23.3%) | 43 (32.6%) |         |
| No                   | 165 (76.7%) | 89 (67.4%) |         |
| BMI                  | 27.5 ± 1.5 | 26.9 ± 1.2 | < 0.001 |
| Diabetes mellitus    |         |        | 0.01    |
| Yes                  | 21 (9.8%) | 25 (18.9%) |         |
| No                   | 194 (90.2%) | 107 (81.1%) |         |
| Coronary disease     |         |        | 0.22    |
| Yes                  | 15 (7.0%) | 5 (3.8%) |         |
| No                   | 200 (93.0%) | 127 (96.2%) |         |
| Respiratory disease  |         |        | 0.19    |
| Yes                  | 11 (5.1%) | 3 (2.3%) |         |
| No                   | 204 (94.9%) | 129 (97.7%) |         |
| Type of vaccine      |         |        | 0.69    |
| Sinovac              | 133 (61.9%) | 85 (64.4%) |         |
| Beijing biological   | 49 (22.8%) | 25 (18.9%) |         |
| Wuhan biological     | 33 (15.3%) | 22 (16.7%) |         |

BMI: Body mass index.

Dosage was used to determine whether or not two doses of SARS-CoV-2 vaccination was effective in preventing infection with the virus. Cancer patients had a seropositivity rate of 83.3% and a median antibody level of 25.8 AU/mL. Seropositivity rate was 96.3% and median antibody level was 31.6 AU/mL in healthy individuals. Cancer patients had significantly lower seropositivity rate and antibody levels when compared with the non-cancer group (P < 0.001, Table 3). We also found no significant variation in the antibody values among different vaccines in both cancer patients and healthy people (P > 0.05, Table 3). Additionally, the immune response may be reduced by chemotherapy and immunotherapy. As a result of active chemotherapy, immunotherapy, and targeted therapy, 66.7%, 74.1%, and 83.3% of patients were seropositive, respectively, as compared to 94.1% in non-treated patients. The efficacy of vaccination was decreased significantly in patients on chemotherapy, immunotherapy, and targeted therapy compared to non-treated patients (Table 4, P > 0.05).

DISCUSSION

In this multicenter study, cancer patients were studied to determine the short-term side effects and effectiveness of SARS-CoV-2 vaccines given that current cancer treatments may have an effect on these outcomes. After receiving the second dose, there was not a statistically significant variation in the incidence of adverse responses between the groups. According to the findings of this study, as
compared to healthy people, the cancer patients had a lower rate of local pain and a higher rate of tiredness. The incidence of other adverse effects was also compared between the two groups, but there were no significant difference between them. We also found an 83.3% seropositivity rate in the cancer patients and a 96.3% seropositivity rate in healthy people. Antibody levels and seropositivity rates were significantly lower among cancer patients than among healthy subjects. Hence, our study indicated that two dosages of SARS-CoV-2 vaccine administration is effective and safe in cancer subjects.

Because of the large number of people who were vaccinated with SARS-CoV-2 vaccine, more and more studies have focused on the rate of vaccine-related adverse effects\[7,8\]. A latest systematic review that comprised eleven studies found that all adverse responses after COVID-19 vaccine administration were mild to moderate, and that few severe reactions were not connected to the vaccination\[7\]. Since there was no clear efficacy and safety evaluation for cancer patients after SARS-CoV-2 vaccine administration in China, high vaccine hesitancy was exhibited in the cancer patients. A European and Hong Kong survey also indicated that most cancer patients were unwilling to be vaccinated or hesitated\[9,10\]. The present study demonstrated that patients suffering from cancer were not at risk when given the SARS-CoV-2 vaccine, and showed no increase in the rate of vaccine-related adverse effects. The results were similar to the previous studies in different countries and on different SARS-CoV-2 vaccines\[1\].

Table 2 Adverse effect after the first and second doses of the vaccine

| Characteristic | Healthy     | Cancer      | P value |
|---------------|-------------|-------------|---------|
| Overall incidence | 34.4% (74/215) | 28.0% (37/132) | 0.215  |
| Tired         | 8.8% (19)  | 15.9% (21)  | 0.045  |
| Headache      | 12.1% (26) | 12.9% (17)  | 0.829  |
| Local pain    | 17.2% (37) | 9.1% (12)   | 0.035  |
| Fever         | 10.7% (23) | 7.6% (10)   | 0.336  |
| Erythema      | 8.4% (18)  | 6.8% (9)    | 0.600  |
| Myalgia       | 7.0% (15)  | 6.1% (8)    | 0.799  |
| Diarrhea      | 5.1% (11)  | 5.3% (7)    | 0.939  |
| Nausea        | 7.4% (16)  | 3.8% (5)    | 0.166  |
| Chills        | 3.7% (8)   | 3.8% (5)    | 0.975  |

Table 3 Vaccine features and antibody levels of the study population

| Characteristic                  | Healthy     | Cancer      | P value |
|---------------------------------|-------------|-------------|---------|
| Antibody level (mean ± SD)      | 31.6 ± 4.8  | 25.8 ± 3.2  | < 0.001 |
| Seropositivity                  |             |             | < 0.001 |
| Positive (≥ 10 AU/mL)           | 96.3% (207/215) | 83.3% (110/132) |         |
| Negative (< 10 AU/mL)           | 3.7% (8/215) | 16.7% (22/132) |         |
| Type of vaccine                 |             |             | 0.206   |
| Sinovac                         | 97.0% (159/164) | 83.2% (89/107) |         |
| Beijing biological              | 95.5% (42/44) | 78.9% (15/19) |         |
| Wuhan biological                | 85.7% (6/7)  | 85.7% (6/7)  |         |

Table 4 Seropositivity rates of cancer patients after severe acute respiratory syndrome coronavirus 2 vaccination according to treatment status

| Characteristic | Seropositivity |
|----------------|----------------|
| No therapy     | 94.1% (43/51)  |
| Targeted therapy | 83.3% (30/36) |
| Immunotherapy  | 74.1% (20/27)  |
| Chemotherapy   | 66.7% (12/18)  |
Shulman et al\textsuperscript{[2]} also reported that patients with cancer were compared with those without cancer in reported adverse events, and active cancer treatment had little impact on adverse event profiles.

The most common symptom reported by healthy people was local pain at the injection site, which was significantly less common among cancer patients. It could be that cancer patients have a higher tolerance for pain after long-term treatment by intravenous injection. Additionally, tiredness was the most common complaint of cancer patients, and its incidence was higher significantly than that in the healthy people. Maybe, patients with cancer suffer from fatigue due to advanced age and weakened bodies than those in the general population. Hence, cancer patients need more rest after SARS-CoV-2 vaccine injection.

For efficacy evaluation, the seropositivity rate was as low as 83.3\% in cancer patients, which was significantly lower than that in healthy people in this study. Further antibody detection showed that patients with cancer had lower IgG antibody levels than individuals without cancer. Ariamanesh et al\textsuperscript{[11]} reported that the seropositivity rate also decreased in patients with malignancies. Similar results also were demonstrated in a Turkey study\textsuperscript{[1]}. In a recent study, Goshen-Lago et al\textsuperscript{[12]} reported that the SARS-CoV-2 BNT162b2 vaccine appeared to be safe and achieve satisfactory serologic status in patients with cancer.

Meanwhile, immune reactions to SARS-CoV-2 vaccination can vary depending on the stage of cancer therapy that the patient is currently receiving. In the present study, the lowest seropositivity rate was 66.7\% after active chemotherapy treatment. Cancer patients who are receiving vigorous chemotherapy and immunotherapy may have a reduced cellular immune reaction, which could be the cause of this immunity suppression. Hence, whether additional doses or strengthened vaccine injections are required needs to be explored in future studies.

There were a few shortcomings with this research. To start, the sample size was low, therefore further research with larger sample sizes is required to investigate the efficacy and safety of SARS-CoV-2 vaccines in cancer patients. Second, we evaluated the efficacy of participants just by detecting the IgG antibody levels, and IgM antibody levels should be assessed in the future study. Third, the current investigation only covered the short-term side effects and efficacy of SARS-CoV-2 vaccines in patients with cancer. To evaluate the effects of vaccines and antibody levels in the prevention of disease, a long-term investigation is required.

**CONCLUSION**

According to the presented findings, two-dose SARS-CoV-2 vaccines in cancer patients are effective and safe. The most prevalent side effects among cancer patients are fatigue, headaches, and localized pain. Cancer patients’ seropositivity rates and IgG antibody levels are lower than those of healthy individuals. Active chemotherapy and immunotherapy maybe affect the effectiveness of vaccines. However, the long-term effects of these vaccines are stills unclear. Further studies with larger populations of cancer patients undergoing two-dose SARS-CoV-2 vaccines should be performed.

**ARTICLE HIGHLIGHTS**

**Research background**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine has evolved as the most effective and secure way for protecting healthy individuals against coronavirus disease 2019 (COVID-19). Patients with cancer have been recognized as a highly vulnerable group, and it is of important significance to clarify the risk and efficacy of vaccination. We aimed to clarify and compare the efficacy and safety of SARS-CoV-2 vaccines between cancer patients and non-cancer individuals.

**Research motivation**

The new coronavirus SARS-CoV-2 has produced a global pandemic of COVID-19, and SARS-CoV-2 vaccine was considered to be a preventive way of accomplishing sufficient herd immunity against SARS-CoV-2 infection to eventually stop the COVID-19 pandemic. Current recommendations suggest cancer patients to undergo SARS-CoV-2 vaccination against COVID-19, but safety and effectiveness evidence is insufficient for SARS-CoV-2 vaccination in cancer patients.

**Research objectives**

The present observational study was conducted to assess the efficacy and safety of two-dose SARS-CoV-2 vaccines in cancer patients.

**Research methods**

This multi-center observational study enrolled 132 eligible patients with cancer. Two weeks following
the second vaccination dose, subjects underwent an analogous questionnaire survey. Utilizing a magnetic particle-based chemiluminescence immunoassay, serum levels of anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies were measured to determine the effectiveness of vaccination. IgG levels ≥ 10 AU/mL were considered seropositive.

**Research results**
Local pain at the injection site was the most common side effect, and its incidence was higher in cancer patients than the healthy people (17.2% vs 9.1%; \( P = 0.035 \)). No significant difference in headache, urticaria, or other adverse reactions was noted between patients with cancer and healthy people. The seropositivity incidence and antibody levels were significantly lower in cancer patients (\( P < 0.001 \)). This analysis showed a relatively poorer response rate in patients on active immunosuppressive treatment and elderly cancer patients.

**Research conclusions**
It is effective and safe to accept two-dose Chinese vaccines in cancer patients. Future studies are needed to focus on the efficacy of these vaccines in elderly cancer patients and those on active immunosuppressive treatment.

**Research perspectives**
Further studies with larger populations of cancer patients undergoing two-dose SARS-CoV-2 vaccination should be performed. Longer follow-up is needed to clarify the long-term efficacy and safety profile of two-dose SARS-CoV-2 vaccines in cancer patients.

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**FOOTNOTES**

**Author contributions:** Cai SW and Chen JY contributed equally to this work; Cai SW, Wan R, Pan DJ, and Chen JY designed the research study; Cai SW, Wan R, and Chen JY performed the research; Pan DJ, Yang WL, Zhou RG, and Chen JY contributed new reagents and analytic tools; Cai SW, Zhou RG, and Chen JY analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

**Institutional review board statement:** The study was approved by the Clinical Research Ethics Committees of Anhui Medical University Affiliated with Wuxi Clinical College (Approval number: YXLL-2020-003).

**Informed consent statement:** Before anyone was allowed to take part in the research project, we made sure that they (or their legal counsel) have provided informed consent to conduct the study.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** On reasonable request, the corresponding author can provide access to the utilized and processed datasets for this study.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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