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Original article

Efficacy and safety of SARS-COV-2 vaccines in breast cancer patients: Egyptian experience

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ABSTRACT

Background: Breast cancer is a major public health problem. Covid-19 pandemic impacted all areas of daily life, including medical care. In particular, delivering care for patients with cancer or suspected cancer during the crisis was challenging given the competing risks of death from untreated cancer versus serious complications from SARS-CoV-2, and the likely higher lethality of Covid-19 in immunocompromised patients. This study aims to assess the efficacy and immunogenicity of SARS-COV-2 vaccines in breast cancer patients by evaluating antispike antibodies in vaccinated and non-vaccinated patients and also through assessing the infection with Covid-19 after vaccination in vaccinated patients and non-vaccinated patients. The study also aims to assess the safety of SARS-COV-2 vaccine in breast cancer patients (local and systemic toxicity). **Methods:** Our population consisted of 120 female patients diagnosed with early and locally advanced breast cancer (60 vaccinated and 60 unvaccinated against Covid-19), in the breast cancer unit, clinical oncology department, Ain Shams University Hospitals. All were on oncological systemic therapy (neoadjuvant or adjuvant treatment). The cutoff value of SARS COV-2 antibody is 50 AU/mL (≥ 50 seropositive, <50 seronegative). **Results:** Out of 120 patients, anti-SARS COV-2 antibody seropositivity was found to be 48 in non-vaccinated vs.58 in vaccinated patients (80% vs.96.7%), with ***p***-value =0.0046, which was statistically significant. The median titre in both groups was found to be 1434.5 vs.2500, (***p***=0.0026). In the 120 patients, 26 patients had Covid-19 infection with a significant difference (***p***= 0.0004), with 21 (35%) non-vaccinated vs.5 (8.3 %) vaccinated. In the sixty vaccinated patients, mild local adverse events were reported such as warmness at site of injection in 17 (28.3%) patients, pain (11, 18.3%), swelling (11, 18.3%), itching (8, 13.3%), and redness (6, 10%) representing the least adverse event. The patients experienced mild systemic adverse events, the highest incidence was fatigue (28, 46.7%), then myalgia/arthralgia (17, 28.3%), headache (2, 3.3%), and fever (16, 26.7%). There was no statistical significance association between antispike Ab titre and age, stage, treatment types, and time since last vaccine. **Conclusion:** SARS-COV-2 vaccines are effective and safe in localized breast cancer patients on systemic therapy.

Introduction

The coronavirus disease (Covid-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported at the end of December 2019 and has rapidly spread worldwide [1].

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Individuals with multiple comorbidities and immunocompromised status are known to have worse clinical outcomes and increased mortality from Covid-19 [2].

Global effort has been made to develop different SARS-CoV-2 vaccines using technologies with excellent efficacy and safety profiles in the general population. However, scarce experimental data have been reported on cancer patients [3].

A prospective study assessed the seroconversion rates and anti-SARS-CoV-2 spike protein antibody titers following the first and second dose of BNT162b2 and mRNA-1273 SARS-CoV-2 vaccines in cancer patients. Among 131 patients, 94% achieved seroconversion after receiving two vaccine doses [4].

Another cohort included 102 adult patients with solid tumors undergoing active anticancer treatment and 78 controls who received the second dose of the BNT162b2 vaccine. In the patient group, 92 (90%) were seropositive for SARS-CoV 2 antispike IgG antibodies after the second vaccine dose, whereas in the control group, all were seropositive. The median IgG titer in the patients with cancer was significantly lower than that in the controls (1931vs 7160 AU/mL; $p <. 001$) [5].

In a retrospective study, which aimed to determinate anti-SARS-CoV-2 spike protein antibody titers among non-vaccinated versus vaccinated solid tumor (n=269) and hematologic patients (n=172) who were under clinical observation or under treatment, the rate of patients with antibody levels ≥15 BAU/mL was significantly higher in patients who completed the vaccination compared to those who did not (86.4% vs.47.1%, $\boldsymbol{p} < 0.0001$) ($\boldsymbol{p} < 0.0001$) [6].

Breast cancer is the most common cancer in women worldwide [7], therefore there is a need to assess the efficacy and toxicity of vaccines in breast cancer patients.

This study aimed to assess the efficacy and immunogenicity of SARS COV 2 vaccines in breast cancer patients by evaluating anti spike antibodies in vaccinated and non-vaccinated patients and also through assessing rate of infection with covid after vaccination (in vaccinated patients) and in non-vaccinated patients. The study also aimed to assess the safety of SARS COV 2 vaccine in breast cancer patients by evaluating systemic and local side effects of the vaccines in this population (local and systemic toxicity).

Patients and methods

Study design and study population

This study was a prospective observational comparative study. It was conducted at the Breast Cancer Unit in clinical oncology department, Ain Shams University Hospitals and clinical pathology department, Ain Shams University Hospitals between April 2022 to February 2023.

The study population was non metastatic breast cancer patients on systemic therapy. The sample size was 120 breast cancer patients (60 unvaccinated patients and 60 vaccinated patients with Covid-19 vaccines).

Inclusion criteria

Patients diagnosed with early and locally advanced breast cancer (M0), ECOG 0-2, age >18 years. Patients on active systemic anticancer treatment: hormonal therapy, chemotherapy and targeted therapy.

Exclusion criteria

Patients who have history of autoimmune diseases, receiving immunosuppressant therapies such as steroids or patients with second primary tumors.

In this study, patients with inclusion criteria were diagnosed with early and locally advanced breast cancer. Adverse reactions were evaluated at time of serum collection.

Patients were classified to 2 groups: group 1 non vaccinated cancer patients against Covid-19 (who didn't receive the vaccine, refused vaccination, or had a past history of allergic reactions against other vaccines) **[6]**, and group 2 vaccinated against Covid-19. The follow up period for the vaccinated group was 3 months after 2nd (last) vaccine dose.

Sample collection

A single blood sample of 5 ml was collected from each individual (vaccinated and non-vaccinated by means of a venous puncture and then was placed in tubes (with a code number). Anti-SARS-CoV-2 S (ant spike) antibody levels were determined from serum samples withdrawn from all patients enrolled in the current study as follows: in unvaccinated patients: the serum samples were withdrawn immediately, but in vaccinated cancer patients: the serum samples were withdrawn at least after 15 days from second vaccination.

The cutoff for seropositivity of SARS-CoV 2 antispike IgG antibodies was defined as 50 or greater AU/mL; this cutoff was chosen in a study by **Massarweh et al.** evaluating the seropositivity of antispike antibodies post vaccination (seropositive >/= 50, seronegative <50) [5].

Sample size

by using 11 program for sample size calculation, setting confidence level at 90%, margin of error +/- 0.15, and after reviewing previous study results **(Singer et al.,)** who showed that the rate cancer patients with antispike antibodies level was higher in Covid-19 vaccinated patients (86.4%) than non-vaccinated (47.1%) and after considering 10% loss to follow up; A sample size of at least 120 breast cancer patients (60 patients vaccinated with Covid-19 vaccine and 60 patients non-vaccinated) will be sufficient to achieve study objective [6].

Outcome evaluation

1ry outcome: The rate of seropositivity of anti-spike antibodies in cancer patients who didn't receive the vaccine (group 1) and patients who received the vaccine (group 2). Infection with Covid-19 (proved with PCR, labs and CT chest) (in vaccinated vs.non vaccinated) [8].

2ry outcome: Toxicity assessment from vaccine (local and systemic); Systemic toxicity was assessed according to National cancer institute-Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0. [9]. Identify association between certain patients' characteristics (age, stage, treatment type) and the antibody titer.

Statistical analysis

The collected data were revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS V20 for windows). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Mean, standard deviation (± SD), minimum and maximum values (range) for numerical data, frequency and percentage of non-numerical data. P-value: Statistical significance was defined as p <0.05.

Results

In this study, we included 120 breast cancer female patients, non-metastatic, on systemic treatment. 60 patients were non vaccinated and 60 were vaccinated.

The two studied groups were well balances in comorbidities, age, stage, types of treatment received, as shown in **(Table 1)**.

The median time from last vaccine dose to sample withdrawal day was 251 days. Mean 237.2, SD: 105.41 days

In group 2**,** the vaccinated patients recruited were vaccinated with different vaccines; Astrazeneca 17 (28.3%), Johnson 4 (6.7%), Moderna 1 (1.7%), Pfizer 8 (13.3%), Sinopharm 14 (23.3%), Sinovac 14 (23.3%), Sputnik 2 (3.3%).

As for the sixty vaccinated patients, they experienced mild local adverse events such as warmness at site of injection in 17 patients, representing (28.3%) of patients, pain 11 (18.3%), swelling 11 (18.3%), itching 8 (13.3%), and redness 6 (10%) representing the least adverse event.

After receiving the anti SARS COV2 vaccines, the patients experienced mild systemic adverse events, the highest incidence was fatigue 28 (46.7%), then myalgia/arthralgia 17(28.3%), headache 2 (3.3%), and fever 16 (26.7%). None of our patients experienced any sense of nausea and vomiting, chills, diarrhea, or hypersensitivity post vaccination.

One hundred and six patients out of 120 patients were seropositive. Seropositive group 1 vs.group 2 was found to be 48 vs.58 pts (80% vs.96.7%) (p=0.0046) which was statistically significant.

The median antispike antibody titre in group 1 vs.group 2 was found to be 1434.5 vs.2500, with lowest value: 0.4 vs.27.18, and highest value: 2500 Vs.2500 (95% CI: 0 to 900, p=0.0026). This emphasizes that antibody titres were higher in vaccinated than non-vaccinated group.

We also evaluated the efficacy of Covid-19 vaccines clinically; In the 120 patients, 26 patients had Covid-19 infection in group 1 vs.group 2 was found to be 21 vs.5 pts (35% vs.8.3 %), p= 0.0004.

Patients who were hospitalized due to Covid-19 infection in group 1 vs.group 2 groups were 3/21(14.3%) vs.1/5(20%) (p=1) which was non-significant

Patients who had cardiovascular consultations were 9 out of 120 patients**,** group 1 vs.group 2 patients: 3/60 (5%) vs 6/60 (10%) patients with a p value: 0.3, also was not significant.

Then we analyzed the patients who had CVS consultations out of the patients who had Covid-19 infection throughout the study. group 1 vs.

group 2 was 2/21 (9.5%) vs.1/5 (20%), ***p***= 0.4884 (non-significant).

Thirty-seven out of 86 patients receiving chemotherapy, had treatment delays, with a percentage of group 1 Vs. group 2: 23 Vs 14 (62.2% Vs.28.6%). (***p*= 0.002).

Treatment interruption in chemotherapy group due to infection with Covid-19 was in group 1 vs. group 2: 9/23 Vs 3/16 (39.1% Vs.18.8%) (***p*** = 0.291**).** Still the non-vaccinated group 1 has higher incidence of treatment interruption due to Covid-19 infection, but this was not statistically significant.

In chemotherapy group, patients who experienced neutropenia during their sessions were 19 out of 86 patients. group 1 Vs. group 2: 12/37 Vs 7/49 pts (32.4% Vs 14.3%) ***p***= 0.0459**,** which was statistically significant.

Out of 86 patients receiving chemotherapy, 22 (25,6%) patients had dose reduction. group 1 Vs. group 2: 11(29.7%) Vs.11(22.4%) pts (***p*** = 0.4462).

Dose reductions were due to neutropenia or other causes such as diarrhea, peripheral neuropathy, etc… Patients who experienced dose reduction due to neutropenia in group 1 Vs. group 2 were 8(72.7%) Vs.5(45.5%), with ***p*** **=** 0.38699. There was a difference, but not statistically significant.

Durability of vaccine effect

Definition

binding antibody levels in relation to time (from vaccination to time of sample) [10].

The result was negative and non-significant as follows with a spearmen coefficient: -0.249, ***p*=0.0553**, 95% CI -0.47 to 0.0055 although as we can see in **figure (4)**, the more time passes and duration increase from time of vaccination, the line representing antispike Ab decrease in titre, and it was very close from being statistically significant. Binding antibody levels decreased over time.

There was no statistically significant correlation between antispike Ab titre and age with a ***p***=0.866**.** Correlation between antispike antibodies and stages of breast cancer was not statistically significant with a ***p***=0.10095**.**

There was no significant correlation between antispike antibodies and different treatment types with ***p*** =0.55069**.** Nevertheless, as we can see median titre differs between hormonal and target therapy 2500 Vs. chemotherapy and chemotarget (2100 and 1601 BAU/mL, respectively). This point needs to be investigated with a larger sample size and more research.

Table 1. Descriptive data of our population.

	Total	**Unvaccinated Group 1**	**Vaccinated Group 2**	***P-value q5***
Age	Median: 51 years old	n=60 median: 52	n=60 median:50	
Comorbidities				**P = 0.2577**
M.F	76 (63.3%)	35	41	
DM	25 (20.8%)	15	10	
HTN	30 (25%)	15	15	
Cardiac	4 (3.3%)	1	3	
Asthmatic	5 (4.2%)	4	1	
Family History (cancer)	+ve 28 (23.3%)	12	16	**P = 0.3899**
Menopause				**P= 0.3566**
Pre	64 (53.3%)	31	33	
Post	54 (45%)	27	27	
peri	2 (1.6%)	2	0	
ECOG				**P = 1**
0	2 (1.7%)	1	1	
1	110 (91.7%)	55	55	
2	8 (6.7%)	4	4	
Stage				**P = 0.8977**
I	5 (4.2%)	2	3	
II	52 (43.3%)	26	26	
III	63 (52.5%)	32	31	
Treatment during sample withdrawal				**P = 0.2473**
Neoadjuvant	40 (33.3%)	17	23	
Adjuvant	80 (66.7%)	43	37	

Treatment types				**P = 0.08**
Chemotherapy	71 pts (59.2%)	32	39	
Chemo-target	15 (12.5%)	5	10	
Hormonal	26 (21.7%)	18	8	
Target	3 (2.5%)	1	2	
Target-hormonal	5 (4.2%)	4	1	

M.F: Medically free; DM: diabetes mellitus; HTN: hypertension.

Table 2. Correlation between treatment type and antispike antibody titre.

Treatment type/ AntiS	**n**	**Minimum**	**25th percentile**	**Median**	**75th percentile**	**Maximum**
Chemotherapy	71	0.4	640.65	2100	2500	2500
Chemo-target	15	3.55	1056.75	1601	2500	2500
Hormonal	26	27.18	772.8	2500	2500	2500
Target	3	2500	2500	2500	2500	2500
Target-hormonal	5	342.9	459.075	1601	2500	2500

Figure 1. Bar chart illustrating percentages of local side effects post SARS COV 2 vaccines.

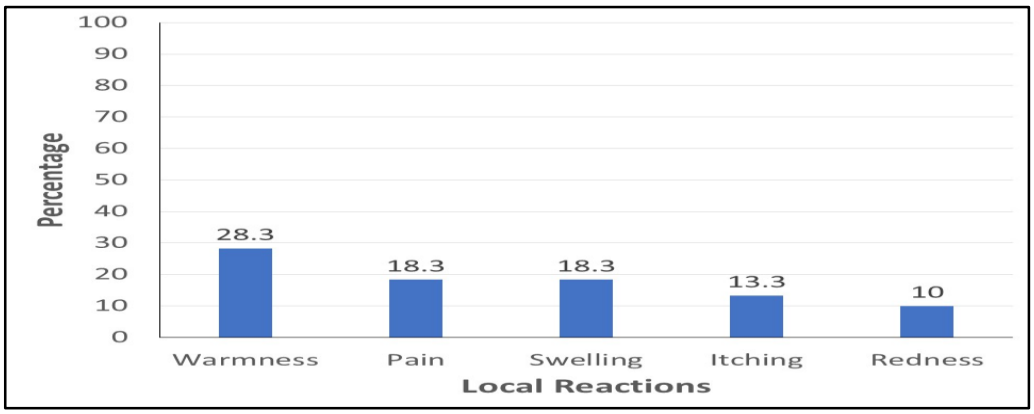


Figure 2. Bar chart illustrating percentages of Systemic side effects post SARS COV 2 vaccines

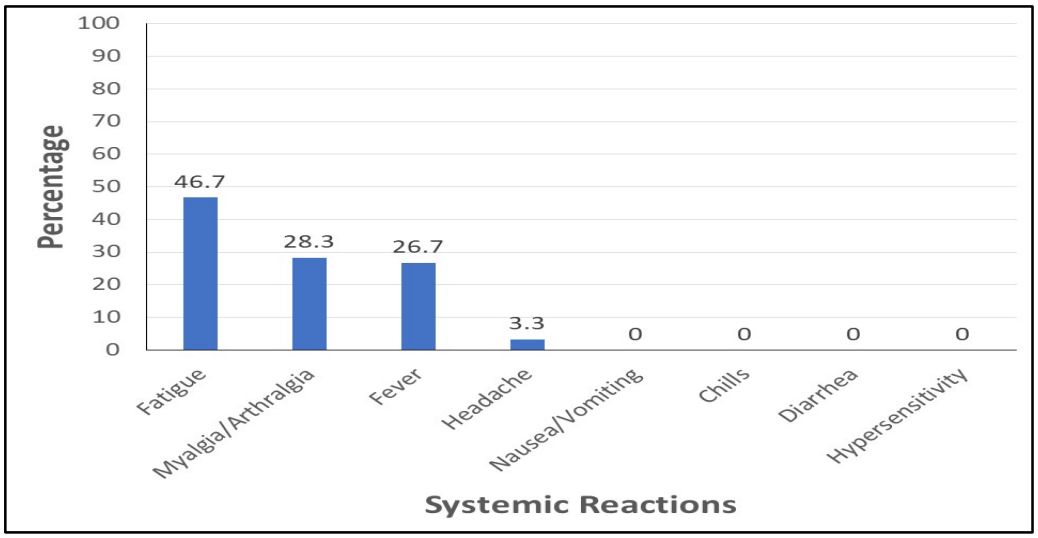


Figure 3. Dot plot comparing ant spike antibody titre levels in both groups.

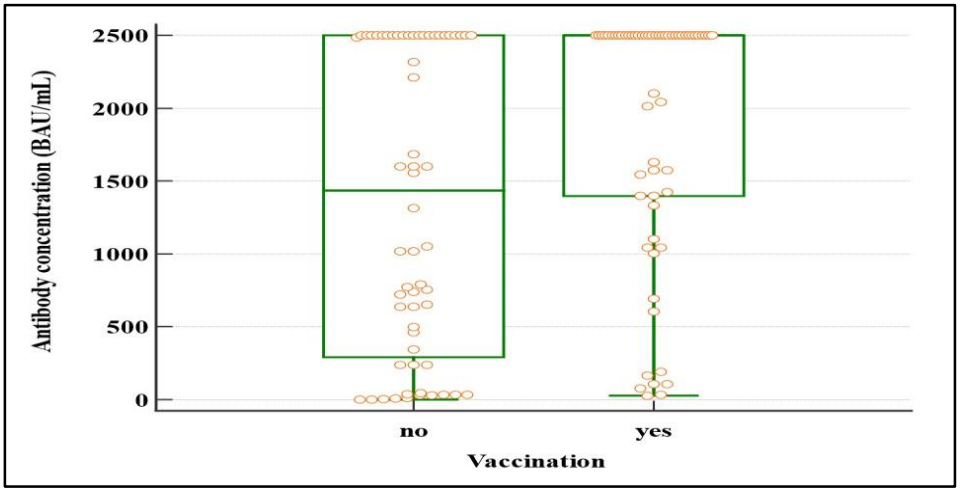
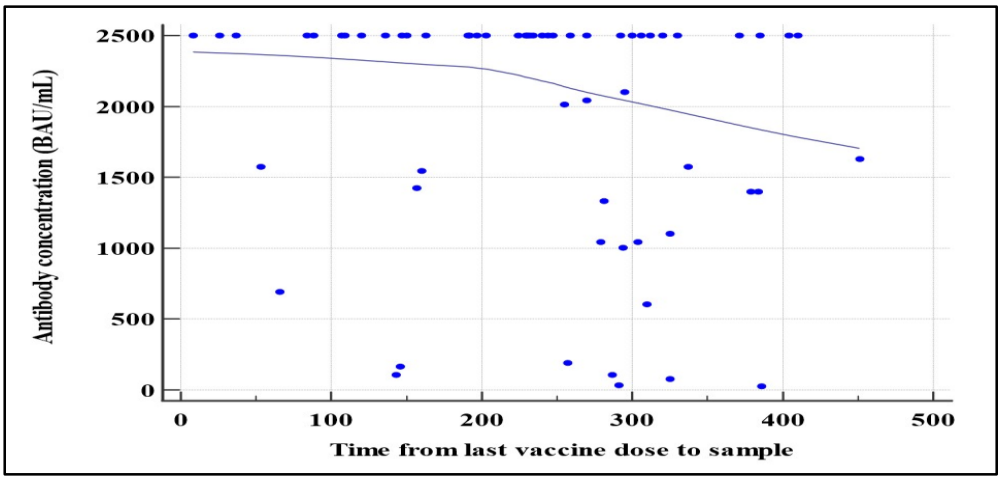


Figure 4. Illustration the correlation between time from (last vaccine date) to (sample withdrawal date) and anti-spike antibody titre.



Discussion

Our study examined the efficacy of SARS-COV-2 vaccines through the evaluation of antispike antibody IgG titre at least after 15 days post vaccination in breast cancer patients on systemic adjuvant and neoadjuvant therapy.

In our study the rate of seropositivity in group 1 vs. group 2 was 80% vs.96.7%, ***p***=0.0046, which was statistically significant and the median antispike in group 1 vs. group 2 was found to be 1434.5 vs.2500, (95% CI: 0 to 900, ***p***=0.0026).

This was in line with **Singer et al.** who evaluated in a total of 441 patients anti-SARS-CoV-2 S antibody titers routinely to patients who were vaccinated or not vaccinated. The non-vaccinated was considered as the control group [6]. Anti-SARS-Cov-2 S antibody levels ≥15 BAU/mL, indicative of the presence of neutralizing antibodies [*11*], were obtained in 134/171 solid tumor (78.4%) patients. The rate of patients with antibody levels ≥15 BAU/mL was significantly higher in patients who completed the vaccination compared to those who did not (86.4% vs.47.1%, ***p*** < 0.0001) [6].

These results reflect that even non vaccinated group had a high level of antispike antibody titre, although there was no history of Covid-19 infection before sample withdrawal; this could be due to possibility of having previous subclinical infection with Covid-19.

In the present study, the median time from last vaccine dose to sample withdrawal day was 251 days. Our results disagreed with **Ligumsky et al.**

who conducted a retrospective study including 326 patients with solid tumors treated with anti-cancer medications following two doses of the vaccine. The median time from second BNT162b2 vaccine dose to antibody testing was 78 days (range = 21-115 days) [10]. The median time in our study was much longer. This could be explained by the fact that this test wasn't routinely done in our center.

In the present work, there was also no correlation found between antispike antibody titre and other additional factors such as age, time to IgG and treatment type.

These findings agreed with **Waldhorn et al**. who tested their patients 166 ± 29 days after second vaccination dose (187 days from the first dose). They reported that 79% (n = 122) of the patients exhibited positive serologic test results, analysis by age, sex, or disease stage yielded no significant difference in serology titer, but remained above threshold value [12].

On the other hand, **Linardou et al.** categorized their population with age, showing that patients aged 18–49 had higher antibody rates compared to those aged 50 and over (median value 1060 versus 491.5, ***p*** = 0.004). This was not consistent with our study [13].

As for the local side effects our patients experienced, site warmness was reported in 28.3 % representing the highest percentage of side effects, followed by pain and swelling (18.3% each), itching (13.3%), and redness (10%) representing the least adverse event. Moreover, our patients experienced mild systemic adverse events, the highest incidence was fatigue 28 (46.7%), then myalgia/arthralgia 17(28.3%), headache 2 (3.3%), and fever 16 (26.7%).

A study done by **Goshen-Lago et al.** reported that the most common local adverse events after the second doses of the BNT162b2 vaccine among their patients (232 cancer patients and 261 healthy controls) were as follows: pain at the injection site (69%), warmness (9%), redness (8%), and swelling (4%). The most commonly reported systemic reactions were fatigue (24%), muscle and joint pain (13%), and headache (10%); 1% of the patients reported a fever event (temperature, >38°C) [14]. These results were almost similar to our study except that fever was found in 26% of our population, but resolved after 1 day with antipyretics and rest. This can be explained that our study includes a more heterogenous types of vaccines. However, in both studies there was no grade 3-4 side effects from vaccines according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [9].

In our study, lower antibodies levels were also observed in chemotherapy [median Ab= 2100 AU/mL] and chemo-target [median Ab=1601 AU/mL], in comparison with hormonal group [median Ab= 2500 AU/mL], and target therapy [median Ab=2500 AU/mL].

This was in line with other studies. A prospective cohort study at two cancer centers in the US and Switzerland assessed patients with solid and hematological malignancies who received either BNT162b2 or mRNA- vaccine on systemic therapy. Significant difference in antibody response was noted between the various anticancer treatment modalities. Patients receiving no therapy (i.e., clinical surveillance) or endocrine therapy had the best outcomes, with high seroconversion rates (98%–100%) and excellent median antibody titer (>2,500 AU/mL)**.** Significantly lower levels of antibody titer were observed for those who received chemotherapy [median Ab =611 AU/mL, ***p***=0.019] and monoclonal antibody therapy [median Ab =152, p=0.029] [4].

Agbarya et al. evaluated the efficacy of the BNT162b2 mRNA Covid-19 vaccine in 73 cancer patients on chemotherapy versus 215 non-cancer group. They found that 17 (23.3%) of the cancer patients were seronegative compared to three (1.4%) of the non-cancer group (***p*** < 0.001). Median immunoglobulin levels were significantly lower in the chemotherapy-treated patients**:** 1361 AU/mL versus 4100 AU/mL for controls (***p*** < 0.001)**.** Chemotherapy has a known inhibitory effect on the immune system**,** one of which is lymphocytopenia. However, cancer patients receiving immunotherapy and targeted therapy had similar serologic response as control group **[**15].

In our study, out of 86 patients receiving chemotherapy, 37 patients (43%) had treatment delays in group 1 Vs. group 2 with a percentage of: 23 Vs 14 (62.2% Vs.28.6%) (***p*** **=** 0.002). Also 19 out of 86 patients experienced neutropenia during their sessions; group 1 Vs. group 2 was: 12/37 Vs 7/49 (32.4% Vs 14.3%), (***p*** **=** 0.0459).

In another study, delay of anticancer treatment two weeks after vaccination occurred only in nine (6%) patients, all of them were under chemotherapy treatment. Treatment delay was due to neutropenia (n = 7), mild thrombocytopenia (n = 1), and neutropenia with herpes labials (n= 1). All

neutropenic patients had gradual decline before vaccination or neutropenia in other cycles. Treatment was renewed within a week in all patients. This delay was a single treatment delay episode in the timeline of these patients [12].

The major strength point in our study was that we included 120 breast cancer patients, all non-metastatic, on systemic therapy, trying to decrease the number of variables. All other studies evaluating the same subject were very heterogenous; their population was on different solid and hematologic cancers**.** They included different types of cancer and included localized and metastatic patients. Even some of them included patients on different types of anticancer treatments and patients on surveillance, off treatments.

Of course, using one vaccine in our study was difficult because of the vaccine supply constraints. At the same time, the distribution of used vaccines wouldn't allow the comparison between the different types of vaccines. The side effects and the antibody responses vary from one vaccine type to another, so the vaccine type is an overlooked factor we ignored in our study result and analysis; which is a major drawback in our study, and this point needs further research.

However, in our study, we observed higher antibody titre in patients who received Pfizer than patients who received AstraZeneca vaccines.

This was in line with another prospective, multi-center study by **Barnes et al**. Functional humoral and T cell responses after Covid-19 vaccination were evaluated in patients receiving immune-suppressive therapy including cancer patients. BNT162b2 (Pfizer) was associated with higher antibody responses compared to ChAdOx1 nCoV-19 (AstraZeneca) vaccination**.** They report 474 SARS-CoV-2 infection episodes, including 48 individuals with hospitalization or death from Covid-19. Decreased magnitude of serological response was associated with severe Covid-19 **[16].**

Conclusion

SARS-COV-2 vaccines are recommended for early and locally advanced breast cancer patients on oncological systemic therapy, with high efficacy and safety. SARS-COV-2 vaccines prevent treatment delays in this curable disease. There was a statistically significant higher incidence of Covid-19 infection incidence in non-vaccinated patients.

Antispike antibody IgG is an effective and easy serological test to assess vaccines protective effect for cancer patients. It was statistically significant higher in vaccinated Vs non-vaccinated patients.

Our future recommendation is to investigate more in the durability of the SARS-COV-2 vaccines in breast cancer patients; this could lead to plan shorter intervals for booster doses in this vulnerable population.

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All anti SARS COV-2 vaccines were provided for free as subcutaneous injections from the ministry of health and population in Egypt.

Author contributions

All the authors contributed to conceptualization and the study design. Data collection was done by MYC and was supervised by DAE. Data analysis was done by HMA and NAE, while all the authors contributed equally to data interpretation.Manuscript drafting was done by MYC while MSK, DAE, NAE, and AMG have revised the manuscript. All the authors approved the final form of the manuscript.

Ethical approval

The study protocol was revised and approved by the research ethics committee Clinical Oncology department, Ain Shams University Hospital and it was conducted according to the 1964 Declaration of Helsinki and its later amendments code (No FWA 000017585. All patients were educated about the study protocol and were required to sign written informed consents prior to participation.

Conflict of interest

All the authors declare no conflict of interest.

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