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Research Report

Surveillance of gynecologic cancer patients post-COVID-19 vaccine: Are CA-125 levels reliable?

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ABSTRACT

Objective: The COVID-19 vaccine is known to instigate an inflammatory response that impacts cancer testing. We aimed to evaluate carbohydrate antigen 125 (CA-125) trends in gynecologic oncology patients in surveillance following COVID-19 vaccination to inform clinical practice.

Methods: This was a single institution retrospective study of patients who received a COVID-19 vaccine while undergoing surveillance of gynecologic cancers with serial serum CA-125 measurements. CA-125 levels from the three months before and after vaccination were included in analysis. Differences between mean and median pre- and post-vaccination CA-125 levels for each patient were calculated. The mean and median of these differences were calculated, as well as the distribution of change. Demographic and cancer-related variables were also recorded.

Results: Twenty-six patients who received a COVID-19 vaccine and were followed with surveillance serum CA-125 levels were identified. The mean age was 68.2 years; 92 % received a two-vaccine series. Forty-six percent had endometrial cancer and 54 % had ovarian cancer. The mean change from pre- to post-vaccine mean CA-125 level was 0.16 (±7.17) U/mL and the median change from pre- to post-vaccine median CA-125 level was −0.30 (IQR 3.66) U/mL. The range in change from pre- to post-vaccine mean was −16.50 to 24.00 U/mL, with 73 % of patients between −4 and +4 U/mL.

Conclusion: We found no clinically significant change in CA-125 level after patients under surveillance for gynecologic cancers were vaccinated against COVID-19, suggesting that that the vaccine does not impact the utility of CA-125 as a tool to monitor disease in this population.

1. Introduction

The COVID-19 pandemic continues to impact almost every aspect of patient care, including cancer treatment and surveillance. While the height of the pandemic brought changes in clinical care aimed at protecting patients and providers, understanding the widespread effects of SARS-CoV-2 infection and vaccination on cancer patients is imperative as new standards for "routine" care are established. For example, reports of false-positive axillary lymph nodes on PET/CT studies in breast cancer patients who received the COVID-19 vaccine highlight the importance of describing COVID-related physiologic changes that can impact staging and surveillance evaluations (Skawran et al., 2022; Brown et al., 2021).

Carbohydrate antigen 125 (CA-125) is a transmembrane glycoprotein expressed in amnion and tissues derived from fetal coelomic epithelium. Clinically, CA-125 levels are primarily used to monitor treatment response and detect recurrence of gynecologic malignancies, most reliably in epithelial ovarian cancer (Montagnana et al., 2017). Monitoring of CA-125, when it was known to be elevated at diagnosis, is a standard part of surveillance for women with ovarian cancer in remission (NCCN, 2022).

CA-125 levels can also be elevated in inflammatory states including, but not limited to, pelvic inflammatory disease, tuberculosis, and endometriosis, and are known to be elevated in patients with chronic lung and heart disease (Sevinc et al., 2007; Frigy et al., 2020). Because of the hyperinflammatory state associated with SARS-CoV-2 infection, it is reasonable to suggest that CA-125 levels might also be elevated in cases

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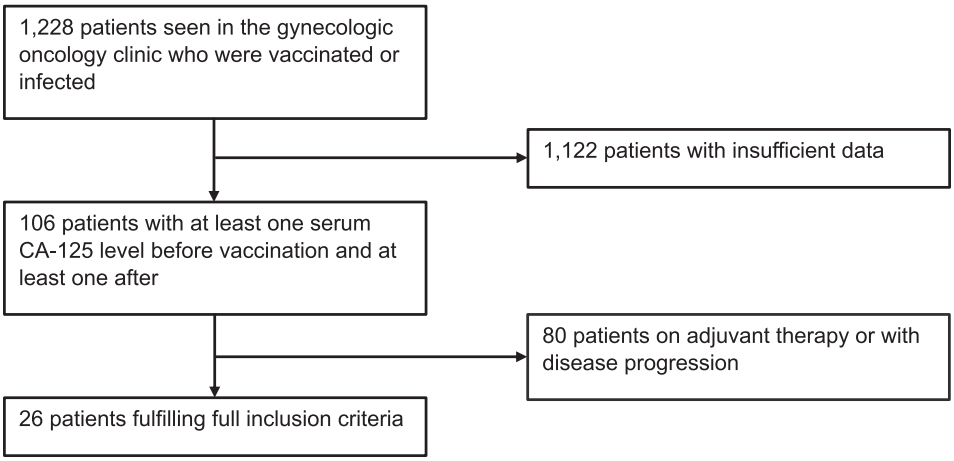

Fig. 1. Study cohort. The final cohort of 26 patients was identified according to the inclusion and exclusion criteria as described.

of COVID-19 (Dokumcu, 2021). Early studies have shown mixed results with respect to the effects of SARS-CoV-2 infection on CA-125 levels in patients without any evidence of gynecological malignancies (Wei et al., 2020; Purut et al., 2021). In one study of 53 women with SARS-CoV-2 infection, no increase in CA-125 was seen, however another study of 252 men and women with SARS-CoV-2 infections showed an increase in CA-125 compared to control patients who had had a CA-125 level drawn prior to the pandemic (Purut et al., 2021; Wei et al., 2020). Notably, the magnitude of increase in CA-125 was higher in patients with more severe infection (Wei et al., 2020).

Less is known about the potential effects of SARS-CoV-2 infection on CA-125 among patients with an established gynecologic cancer diagnosis. A case report of a patient being treated for ovarian cancer noted a transient elevation in CA-125 following SARS-CoV-2 infection without evidence of cancer progression on standard imaging, raising the possibility that SARS-CoV-2 infection may increase CA-125 independent of cancer recurrence or progression (Smith et al., 2020). Another recent report of a patient with ovarian cancer showed a temporary increase in CA-125 following a mild SARS-CoV-2 infection, however it is unknown whether she had simultaneous disease progression (Gunn et al., 2022).

Similarly, the post-COVID-19 vaccination period can be considered as a transient inflammatory state based on commonly experienced symptoms, as well as reactive lymphadenopathy seen on imaging (Brown et al., 2021; So et al., 2021). As such, it is possible that COVID-19 vaccination may also result in transient elevation of serum CA-125 levels. A possible association between SARS-CoV-2 infection or COVID-19 vaccination and elevated CA-125 levels has the potential to confound the treatment and surveillance of patients with gynecologic malignancies.

The aim of this study was to evaluate the CA-125 trends following COVID-19 vaccination in patients in surveillance for gynecologic malignancies to better guide clinical practice as the effects of the pandemic, and now potential for seasonal vaccination, continue.

2. Materials and Methods

2.1. Study design

This was a retrospective study conducted at the UMass Chan Medical School and UMass Memorial Medical Center. Specifically, retrospective chart review was performed and type of malignancy, CA-125 levels, imaging studies evaluating for cancer recurrence and/or progression, and documentation of COVID-19 vaccination was recorded between October 2020 and July 2021. Pathology results and patient imaging, such as CT scans, MRIs, and PET scans were reviewed during this process. Demographic variables included age, BMI, race, and ethnicity. Additionally, diagnosis of diseases that could confound serum CA-125 levels such as heart failure and/or chronic obstructive pulmonary disease were noted. Electronic data regarding clinical symptoms, diagnosis, treatments, and outcomes were all extracted. EPIC, the current electronic medical record system used for UMass Memorial patients, was used to collect the above data.

2.2. Participants

Initial chart review identified patients seen in our gynecologic oncology clinic who had received the COVID-19 vaccine or who had had a confirmed SARS-CoV-2 infection between March 2020 and July 2021. Patients met inclusion criteria if they were in surveillance for a gynecologic malignancy at the time of the study, had at least two CA-125 levels drawn through our gynecologic oncology clinic in the study time period, and had received the COVID-19 vaccine or had a documented SARS-CoV-2 infection. Additionally, at least one of their CA-125 levels must have been drawn prior to vaccination or infection and at least one drawn after. Patients undergoing cancer surveillance that did not include CA-125 trends, patients who had inadequate CA-125 levels drawn during the study period, patients on adjuvant therapy or who had disease progression, and patients who neither received the COVID-19 vaccine nor had a documented SARS-CoV-2 infection were excluded. Vulnerable populations, including patients under age 18, incarcerated patients, and patients with cognitive impairment, were also excluded from this study.

2.3. Statistical analysis

Statistical analyses were performed with Microsoft Excel software. For each patient, the mean CA-125 levels for the three months before and the three months after vaccination were calculated. The difference between the mean pre- and post-vaccine CA-125 level was calculated for each patient, and the mean and median of these differences were calculated. We similarly calculated the median CA-125 level for each patient in the three months before and after vaccination and calculated the difference between these medians. The mean and median of these differences was also calculated. Additional calculations included the mean number of days between the vaccination and the first post-vaccine CA-125 level, the mean number of CA-125 levels included for each patient for each time period, and the distribution of change in means pre- and post-vaccination.

When patients received two doses of a vaccine, the second dose was considered their vaccination date. When the final vaccine was received fewer than three months before the end of July 2021, the post-vaccine timeframe was the time from vaccine to the end of July 2021. CA-125

Table 1
Demographic and oncologic characteristics among study patients. Age and BMI are shown as mean (standard deviation) and all others are number (percent). Percentages may not equal 100 due to rounding.

	Total n = 26
Age (years)	68.2 (12.0)
BMI (kg/m^2)	29.1 (5.4)
Race	
Asian	1 (4 %)
White	24 (92 %)
Other	1 (4 %)
Ethnicity	
Hispanic or Latino	1 (4 %)
Not Hispanic or Latino	25 (96 %)
Vaccine type	
Pfizer	17 (65 %)
Moderna	7 (27 %)
Janssen (J&J)	2 (8 %)
Previous diagnosis of CHF	
No	25 (96 %)
Yes	1 (4 %)
Previous diagnosis of COPD	
No	25 (96 %)
Yes	1 (4 %)
Primary Cancer site	
Endometrium	12 (46 %)
Ovary / Fallopian tube / Peritoneum	14 (54 %)
Cancer grade	
1	6 (24 %)
2	3 (12 %)
3	16 (64 %)
Cancer histology	
Adenocarcinoma, NOS	4 (15 %)
Endometrium	1 (4 %)
Ovary	3 (12 %)
Carcinosarcoma (Endometrium)	1 (4 %)
Clear cell (Ovary)	2 (8 %)
Endometrioid	8 (31 %)
Endometrium	7 (27 %)
Ovary	1 (4 %)
Neuroendocrine	1 (4 %)
Serous	10 (38 %)
Endometrium	3 (12 %)
Ovary / Fallopian tube / Peritoneum	7 (27 %)
Ovary / Fallopian tube / Peritoneum cancer stage	
IIIA2	1 (20 %)
IIIB	2 (40 %)
IIIC	2 (40 %)
Uterine cancer stage	
IA	1 (8 %)
IB	3 (25 %)
II	1 (8 %)
IIIA	3 (25 %)
IIIB	1 (8 %)
IIIC1	1 (8 %)
IIIC2	1 (8 %)
IVB	1 (8 %)
Cancer recurrent prior to March 2020	
No	19 (73 %)
Yes	7 (27 %)

levels were primarily measured at our home institution; some were measured at outside laboratories for patient convenience. These outside measurements were included in analysis if they were entered into our electronic medical record.

Permission to conduct this retrospective chart review study was obtained from the UMass Chan Medical School Internal Review Board (IRB) under study #H00023904. The aforementioned variables were collected and stored in REDCap, a secure web application for building and managing online surveys and databases. This application is password protected and only study personnel had access.

Table 2
Change in mean and median CA-125 level 3 months before and after completing the COVID vaccine series. The change in mean and median CA-125 level from the three months before receiving the final COVID vaccine to the three months after is shown for each patient. The mean difference with standard deviation and the median difference with the interquartile range are also shown.

Patient ID	Change in **mean** CA-125 3 months pre- and post-vaccine (U/mL)	Change in **median** CA-125 3 months pre- and post-vaccine (U/mL)
1	−0.73	−1.00
2	−7.30	−7.30
3	1.00	1.00
4	−2.83	−2.40
5	0.33	0.00
6	−6.00	−1.00
7	−0.25	0.00
8	2.00	2.00
9	−0.61	−0.35
10	1.00	1.00
11	1.67	2.00
12	24.00	24.00
13	−2.60	−2.00
14	−0.17	−0.50
15	1.18	1.15
16	0.73	−0.25
17	−8.00	−7.00
18	−1.00	−1.00
19	2.00	2.00
20	−16.50	−6.10
21	6.20	7.00
22	−1.50	−1.50
23	−3.65	−3.65
24	15.50	15.50
25	2.00	2.00
26	−2.20	−2.00
Mean	0.16	0.83
Std dev	7.17	6.32
Median	−0.21	−0.30
IQR	4.05	3.66

3. Results

We identified 1,228 individual patients who had been seen in the Gynecologic Oncology clinic and who had a SARS-CoV-2 infection and/or received a vaccine during our study period. Of those patients, 106 had at least one serum CA-125 level before vaccination and at least one after. Ultimately 26 patients were identified meeting the full inclusion and exclusion criteria; all were vaccinated, and none had a documented SARS-CoV-2 infection (Fig. 1).

The demographic and oncologic characteristics of the 26 patients included in the study are shown in Table 1. The mean age was 68.2 (±12.0) years and the mean BMI was 29.1 (±5.4) kg/m^2. The majority of patients were white (92 %) and non-Hispanic (96 %). Prior diagnoses of congestive heart failure and chronic obstructive pulmonary disease were rare; one patient had each diagnosis. The majority of patients received a two-vaccine series (65 % Pfizer and 27 % Moderna) and all patients completed the series.

The primary cancer sites were relatively evenly distributed between endometrial (46 %) and ovarian/fallopian tube/primary peritoneal cancers (54 %). Serous cancers were the most common histology (38 %), with more originating from the ovary/fallopian tube/peritoneum than from the endometrium. Endometrioid cancers were the second most common (31 %), with more originating from the endometrium than the ovary. Less common histologies included carcinosarcoma (4 %), clear cell (8 %), neuroendocrine (4 %) and adenocarcinoma, NOS (15 %). Most patients in this cohort had not experienced recurrence of their cancer prior to March 2020 (73 %).

The mean CA-125 for each patient in the three months before and after they received the final COVID-19 vaccine was calculated. The mean number of CA-125 values in the pre-vaccine time period was 3 and

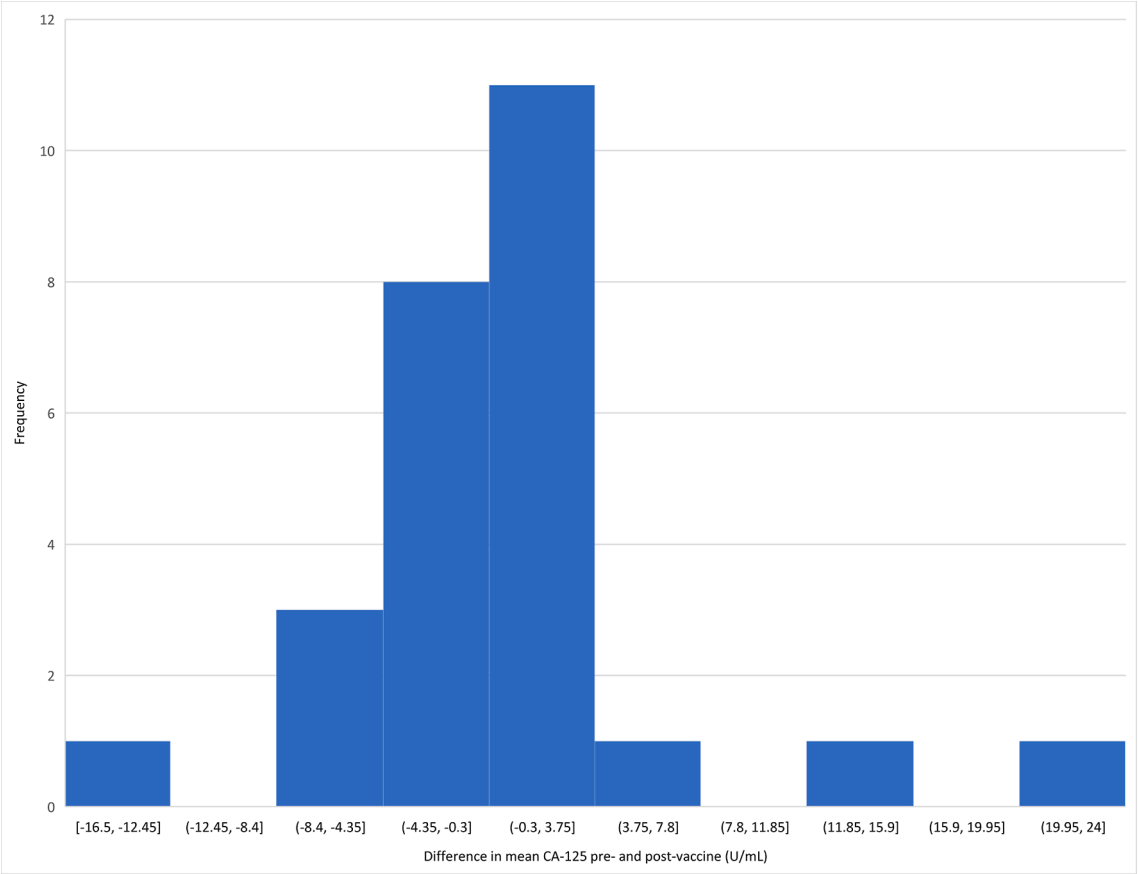

Fig. 2. Distribution of change in mean CA-125 level 3 months before and after completing the COVID vaccine series. The range of change in mean CA-215 levels was divided into ten equal bins and the number of patients falling into each bin is shown.

in the post-vaccine time period was 2 (data not shown). The difference between the means for each patient was calculated. The mean of the changes from pre- to post-vaccine CA-125 level was 0.16 (±7.17) U/mL. The median change in mean CA-125 was −0.21 U/mL with an interquartile range of 4.05 U/mL (Table 2).

Median CA-125 for each patient in the three months before and after vaccination was also calculated, as well as the difference in median change. The mean change in median CA-125 from pre- to post-vaccine CA-125 level was 0.83 (±6.32) U/mL and the median change in median CA-125 was −0.30 U/mL with an interquartile range of 3.66 u/mL (Table 2).

The range in change from pre- to post-vaccine mean extended from −16.50 to 24.00 U/mL, however 19 of 26 patients fell between −4 and + 4 U/mL (Table 2, Fig. 2). The mean time from final vaccine to next CA-125 level was 24.19 (±17.20) days (data not shown).

4. Discussion

We aimed to evaluate for potential impact of COVID-19 vaccination on CA-125 level among gynecologic oncology patients in surveillance. Any impact attributable to vaccination could affect the reliability of CA-125 as a tool to monitor for disease progression in these patients, and it is therefore important that this be investigated. Among the patients in our gynecologic oncology clinic undergoing cancer surveillance with serial CA-125 levels who received a COVID vaccine, the average change in CA-125 level from the 3 months before vaccination to the 3 months after vaccination was minimal at 0.16 U/mL, suggesting that the vaccine does not impact CA-125 level, and particularly that it does not impact the utility of CA-125 as a tool to monitor disease.

We chose the three month timeframe for pre- and post-vaccine measurements because it provided a reasonable balance between biological plausibility of effect of the vaccine on CA-125 level with the number of serum CA-125 tests a patient would have had collected. Shorter timeframes provided fewer CA-125 values, while longer timeframes could potentially dissipate the potential effect resulting from inflammation on the serum CA-125 level or confound the level with sequelae of yet-to-be diagnosed disease progression. Limiting the timeframe to the three months before and after the vaccine did lead to the loss of a large proportion of the patients we initially identified, however we felt that expanding the timeframe to include more patients would simultaneously decrease the plausibility that any identified trend in CA-125 could be related to the vaccine.

Although we initially planned to evaluate for any impact a SARS-CoV-2 infection may have on CA-125 level, none of our patients meeting all inclusion and exclusion criteria had documented SARS-CoV-2 infections; therefore, this was not evaluated. It is certainly possible that the immune response and CA-125 response to an infection could differ from the response to the vaccine. Similarly, it is possible that patients with progressive disease could have a different response in CA-125 to vaccination or infection than patients in surveillance. Notably, in a recent case series of patients with gynecologic cancers, both active and with no evidence of disease, and SARS-CoV-2 infection, most patients had no change or a decrease in CA-125 (Folsom et al., 2022). Of the patients who had a rise in CA-125, it was most appropriately attributed to their malignancy (Folsom et al., 2022). These are encouraging results and support what was found in our study.

Additional limitations of our study include that it is limited to a single institution and has a small sample size. The racial and ethnic make-up of the patient population is also homogenous. Expanding beyond our clinic to include a larger and more diverse population would

increase the accuracy and generalizability of our results. Comparison of CA-125 trends around vaccination in patients with and without gynecologic cancers could also provide further valuable information.

Strengths of our study include the inclusion of patients with both ovarian and endometrial cancers. We also included COVID-19 vaccines from all three manufacturers available to our patients. This study includes data beginning from the introduction of COVID-19 vaccines, and thus represents a unique opportunity for early assessment of effects of the vaccine on patients with gynecologic cancers.

Our data suggests that serum CA-125 values are not affected by COVID-19 vaccination and that CA-125 continues to be a reliable tool to monitor disease in gynecologic oncology patients for whom it is known to be a marker. Based on our findings, we do not suggest delaying CA-125 measurement after receipt of the vaccine. This should be reassuring for both patients and providers as the vaccine continues to be an important component of preventive care.

CRediT authorship contribution statement

Elizabeth Thayer: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Lindsay Walsh:** Investigation, Writing – original draft. **Katherine Leung:** Formal analysis. **Sharmilee Korets:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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