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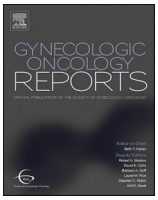

Case series

# CA-125 monitoring in gynecologic cancer patients with COVID-19: A case series

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A B S T R A C T

CA-125 has long been utilized as a surveillance biomarker for gynecologic malignancies but can be elevated in other conditions, including infection. A study of tumor markers in non-cancer patients saw a rise in CA-125 values during severe COVID-19 infections. Given the potential confounding effect this could have on surveillance and treatment planning, we sought to describe the impact of COVID-19 on CA-125 trends in a gynecologic oncology patient population.

We conducted a retrospective chart review of patients treated at a UPMC hospital during the COVID-19 pandemic from March of 2020 through September of 2021. Patients were included for analysis if they had confirmed uterine or ovarian malignancies, a COVID-19 infection and more than one CA-125 value drawn within one year of their COVID-19 diagnosis. The CA-125 values were plotted against the timeline of their COVID-19 infections to assess for trends in CA-125 during and after infection.

There were 17 patients who met the above criteria. Of these 17 patients, three had a rise in their CA-125 trend at the time of their COVID-19 diagnosis. Another three had newly elevated CA-125 values, without a prior documented baseline level, at the time of their infection. In all six of these patients, their CA-125 elevations could be attributed to malignancy. The remaining 11 patients showed stable or decreasing CA-125 values coinciding with their COVID-19 infection.

This case series illustrates that while CA-125 values may increase during an acute COVID-19 infection, cancer remains the most likely cause of a CA-125 increase. Clinical suspicion should remain high for a possible change in cancer status.

## 1. Introduction

Carbohydrate Antigen 125 (CA-125), is a glycoprotein first discovered in the early 1980s. (Bast et al., 1981) Since that time, it has been utilized as a serum tumor marker in the diagnosis and monitoring of ovarian cancer and other gynecologic malignancies. For most laboratories, the upper limit of normal for CA-125 is 35 U/mL, based on the distribution of values in a healthy population. (Shih Ie et al., 2002) When trending CA-125 values, there isn't a well-defined number that would warrant a clinically meaningful change. However, a study by Piatek et al., suggested that a rise in CA-125 by greater than 5 U/mL within the normal range could have prognostic significance. (Piatek et al., 2020) Importantly, CA-125 can be elevated in other malignant processes such as breast, lung, liver pancreatic, uterine, and cervical cancer. (Ruibal et al., 1985; Haga et al., 1986; Niloff et al., 1984 Nov) It has also been shown to be elevated in non-malignant inflammatory conditions including, but not limited to, benign gynecological conditions, inflammatory peritoneal diseases and inflammatory lung processes. (Buamah, 2000; Barouchos et al., 2015) Given its documented fluctuations in inflammatory lung processes, it is intuitive that CA-125 values may be elevated in patients with COVID-19 infections.

In June of 2020, Wei et al published a retrospective study evaluating CA-125 values in 245 hospitalized, non-cancer patients with COVID-19. The patients were separated into mild, moderate, and severe COVID-19 infections. The CA-125 values were noted to be significantly higher in patients with severe infections when compared with patients with mild disease ($18.1 \pm 13.5$ versus $10.5 \pm 4.6$, $p < 0.001$). (Wei et al., 2020) In the wake of these results, a case report was published in June of 2020, describing a transient CA-125 elevation in an ovarian cancer patient during the timeframe of their COVID-19 infection. (Smith et al., 2020) The patient had no other signs of cancer progression that could have otherwise explained the CA-125 increase and the CA-125 value decreased to its previous level with continued monitoring. Given these reported findings, we endeavored to investigate CA-125 trends in our own patients with COVID-19 infections and gynecologic malignancies.

## 2. Methods

After obtaining IRB approval, we performed a single institution case series evaluating CA-125 levels in gynecologic cancer patients with

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COVID-19 infections within the University of Pittsburgh Medical Center (UPMC) from March of 2020 through September of 2021. Eligibility criteria included a confirmed uterine or ovarian malignancy, a COVID-19 infection and more than one CA-125 value drawn within one year of their COVID-19 diagnosis. A Clinical Data Warehouse comprised of all discrete data entered into the electronic medical record was used to for initial identification of eligible patients. Charts for these patients were then manually reviewed by two physicians to identify patients with a uterine or ovarian cancer diagnosis and more than one CA-125 value within one year of their COVID-19 infection. If less than a year had passed since their infection, CA-125 values drawn up until the end of our data collection period (September 15, 2021) were included. Demographic information, baseline cancer information including cancer type, stage at initial diagnosis, histology and grade, current disease status and treatment information were collected. For those with active disease (a new diagnosis of cancer or undergoing therapy), their cancer status was categorized as stable, progressing or responding to therapy. Assessment of disease status was based on changes in tumor marker levels (CA-125), CT imaging and/or physical exam findings as reported in the clinical record. Patients with stable disease had no change in their disease burden during the study period. Patients categorized with progressing disease had indications that their disease burden increased during the study period and patients who responded to therapy showed a decrease in disease burden. If the patient was in post-treatment surveillance, their disease status was categorized as no evidence of disease or newly recurrent if recurrence was diagnosed during or after their COVID-19 infection (Table 1).

**Table 1**
Patient Characteristics.

| | Total (n = 17) | Increasing CA-125 Trend (n = 3) | Newly Elevated CA-125 (n = 3) | Decreasing CA-125 Trend (n = 4) | Stable CA-125 Trend (n = 7) |
|---|---|---|---|---|---|
| **Mean age (standard deviation), years** | 62.41 (6.67) | 64.67 (9.02) | 60 (6.56) | 66.67 (7.37) | 60.88 (5.96) |
| **Race** | | | | | |
| White | 16 (94%) | 3 | 3 | 3 | 7 |
| Black | 1 (6%) | 0 | 0 | 1 | 0 |
| **Cancer Type** | | | | | |
| Ovarian | 13 (76%) | 3 | 2 | 4 | 4 |
| Endometrial | 4 (14%) | 0 | 1 | 0 | 3 |
| **Stage** | | | | | |
| I-II | 6 (35%) | 0 | 2 | 0 | 4 |
| III-IV | 11 (65%) | 3 | 1 | 4 | 3 |
| **Disease Status** | | | | | |
| Active Disease | | | | | |
| Stable | 6 (35%) | 1 | 0 | 3 | 2 |
| Progressing | 3 (18%) | 2 | 0 | 1 | 0 |
| Responding | 3 (18%) | 0 | 3 | 0 | 0 |
| No evidence of disease | 5 (29%) | 0 | 0 | 0 | 5 |
| **Treatment** | | | | | |
| None | 7 (41%) | 1 | 0 | 0 | 6 |
| Cytotoxic | 5 (29%) | 0 | 2 | 2 | 1 |
| Targeted | 2 (12%) | 1 | 0 | 1 | 0 |
| Cytotoxic + Radiation | 2 (12%) | 1 | 1 | 0 | 0 |
| Cytotoxic + Targeted | 1 (6%) | 0 | 0 | 1 | 0 |
| **Comorbidities** | | | | | |
| DM | 6 (35%) | 2 | 1 | 1 | 2 |
| HTN | 8 (47%) | 1 | 2 | 2 | 3 |
| Hypothyroid | 5 (29%) | 0 | 0 | 1 | 4 |
| Other Cancer | 1 (6%) | 1 | 0 | 0 | 0 |
| CHF | 3 (18%) | 1 | 1 | 1 | 0 |
| Stroke | 1 (6%) | 0 | 0 | 0 | 1 |
| CKD | 1 (6%) | 1 | 0 | 0 | 0 |
| PE | 2 (12%) | 0 | 1 | 0 | 1 |

DM: Diabetes Mellitus, HTN: Hypertension, CHF: Congestive Heart Failure, CKD: Chronic Kidney Disease, PE: Pulmonary Embolism.

## 3. Results

Within the UPMC system, 78 patients tested positive for COVID-19 and had CA-125 lab values measured within one year of their infection during the timeframe of our study. Of these 78 individuals, 21 had more than one CA-125 value drawn after testing positive for COVID-19, allowing us to evaluate trends. Upon chart review, 17 of these patients were identified as having uterine or ovarian cancer and were the population of interest for all analyses.

Of the 17 patients with CA-125 trends and gynecologic malignancy, four (23.5%) had endometrial cancer and the remaining 13 (76.5%) had ovarian cancer. Three (17.6%) patients were newly diagnosed with their cancer or a cancer recurrence within 30 days of their COVID-19 infection. Five (29.4.%) had a history of cancer documented but were without evidence of active disease. Four (23.5%) patients had their treatment held or interrupted due to their acute COVID-19 infection.

Within our cohort of 17 patients, there were four distinct CA-125 value trends noted (1) elevation from a previously normal baseline, (2) newly elevated without a previously documented baseline, (3) decreasing from a prior elevated value and (4) stable value. Three patients (17.6%) had a rise from baseline in their CA-125 following their COVID-19 diagnosis. Three other patients 17.6%) had a newly documented, elevated CA-125 value at the time of their COVID-19 diagnosis with an unknown baseline. Of the remaining 11 patients, four (23.5%) patients had a declining CA-125 trend at the time of their COVID-19 diagnosis. Seven (41.2%) had CA-125 values that differed by less that 5 U/mL of their baseline spanning the time of their COVID-19 infection. These patients were deemed as stable CA-125 trends for the purpose of this study.

Patients 2, 5 and 14 (Fig. 1) all had increases in their CA-125 trend following their COVID-19 diagnosis. However, each of these patients also had cancer progression that could also explain the increases in their CA-125. Patient 2 had known, recurrent ovarian cancer, and was on a two-month treatment holiday at the time of her COVID-19 diagnosis due to co-morbid conditions requiring inpatient hospitalization. Just before her COVID-19 diagnosis, she had a PET-CT that noted a PET-avid pelvic nodule as an isolated site of active disease. Her CA-125 values rose from 23 U/mL in the time prior to her PET/CT and prior to her COVID-19 diagnosis to 117 U/mL at the time of her COVID-19 diagnosis. The patient then received stereotactic radiation therapy to her pelvic nodule within a month of her COVID-19 diagnosis and her CA-125 dropped to 11 U/mL and remained stable over the course of the next six months. Patient 5 similarly showed an increase in their CA-125 value following their COVID-19 diagnosis. Patient 5 was in post-treatment surveillance after treatment with liposomal doxorubicin for recurrent disease when her CA-125 increased from 26 U/mL before her COVID-19 diagnosis to 262 U/mL following her COVID-19 diagnosis. Unlike many of the patients in this case series, her COVID-19 associated symptoms were documented in detail. She reported significant COVID-19 symptoms including high fevers and intractable nausea and vomiting from coughing. She never required hospitalization but had a prolonged

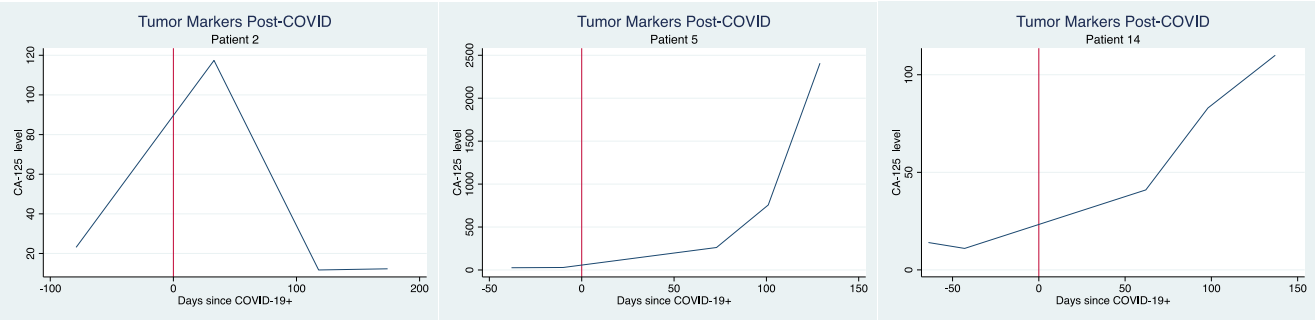


**Fig. 1.** Elevation in CA-125 from a previously normal baseline.

symptom course with her COVID-19 infection. Interestingly, she had no evidence of disease progression on her CT scan that coincided with her COVID-19 infection and her initial CA-125 elevation. However, her CA-125 continued to rise even after she was recovering from her infection, and clinically visible disease was eventually noted on her follow up imaging 6 months following her COVID diagnosis. Like patient 5, patient 14 was in post-treatment surveillance following her primary adjuvant course of carboplatin and paclitaxel. The elevation in her CA-125 was initially gradual, and her surveillance CT scans did not immediately show progression of her disease as the tumor marker values began to rise. The CA-125 trend continued to increase and within six months, the patient had clinically visible disease progression on imaging.

Three patients had their first documented elevated CA-125 value in the setting of a new diagnosis or new recurrence of cancer at the time of their COVID-19 infection (Patients 6, 13 and 15, Fig. 2). Patient 6 had presented to the hospital in the setting of chest pain and shortness of breath and was diagnosed with an acute pulmonary saddle embolus that was initially attributed to her COVID-19 diagnosis. She re-presented to the hospital three weeks later in the setting of heavy vaginal bleeding and was subsequently diagnosed with widely metastatic ovarian cancer. It was during this second visit that she had a CA-125 drawn and was notably elevated at 2,236 U/mL. With the initiation of cancer directed treatment, her CA-125 appropriately began to down-trend. Patient 13 presented to the hospital with diarrhea, abdominal pain and a nonproductive cough. During her clinical work-up, she was ultimately diagnosed with both stage III ovarian cancer and COVID-19. Her CA-125 also began to down-trend once she recovered from her COVID-19 (from 1025 to 615). It further decreased to normal levels once she initiated therapy a month later. Patient 15 had a slightly different course. Her CA-125 was noted to be elevated two months prior to her COVID-19 diagnosis in the setting of a new pelvic mass and a history of surgically treated stage IA endometrial cancer. Importantly, she had not had a CA-125 level drawn at the time of her initial endometrial cancer diagnosis. This pelvic mass was ultimately diagnosed as an endometrial cancer recurrence and was treated with radiation and systemic therapy. Her CA-125 values down trended in accordance with her treatment.

The remaining 11 (64.7%) patients showed decreased (Patients 3,8,9 and 16, Fig. 3) or stable (Patients 1,4,7,10,11,12 and 17, Fig. 4) CA-125 levels when compared before and after their infection. These patients had known ovarian or uterine cancer and were either receiving treatment or undergoing post-treatment surveillance at the time of their diagnosis with COVID-19. None of them had an increase in their CA-125 trend immediately following their COVID-19 infection. One patient (Pt 16) eventually had increases that accompanied disease progression but was remote from their COVID-19 diagnosis. One patient in this category appeared to have an increase in their CA 125 when graphing the lab draws over time (Patient 1, Fig. 4) but the change in value was 0.4 U/mL. This was not considered clinically significant according to the parameters set for this study.

## 4. Discussion

In summary, three patients in our series had a clinically significant rise in their CA-125 from a documented baseline following their COVID-19 diagnosis (Patients 2, 5 and 14, Fig. 1). Three patients had newly elevated CA-125 values at the time of their COVID-19 diagnosis that coincided with a new or recurrent diagnosis of cancer and appropriately decreased with treatment. The remaining patients did not show an increase in their CA-125 following their COVID-19 diagnosis and many even showed a decrease. Ultimately, these trends did not follow the pattern seen in the CA-125 trend in the case report by Smith et al. While it is challenging to know if the COVID-19 played a role in the amount the CA-125 rose, COVID-19 does not seem to independently account for any of the elevations in CA-125 trends in our case series.

CA-125 has long been considered a marker for ovarian and other gynecologic cancers, and an effective way to monitor the progression of disease, but its sensitivity and specificity has the potential to be confounded by its role as a marker of other forms of inflammation. Its role as a marker of inflammation in lung pathologies poses a particular issue for gynecologic cancer patients affected by COVID-19. In Wei et al's paper, describing tumor marker variation in patients with COVID-19 but without cancer, they were able to show that CA-125 was significantly higher in non-cancer patients with severe infections when compared to patients with mild infections (18.1 ± 13.5 U/mL versus

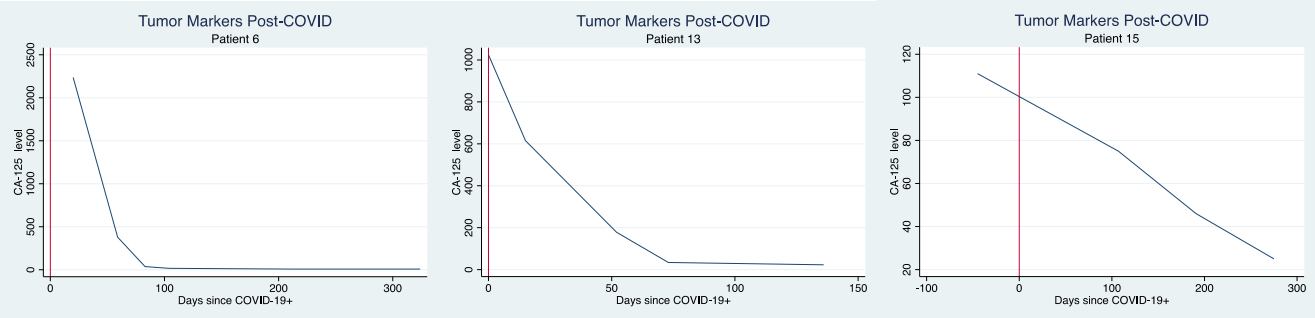


**Fig. 2.** Newly elevated CA-125 without a previously documented baseline.

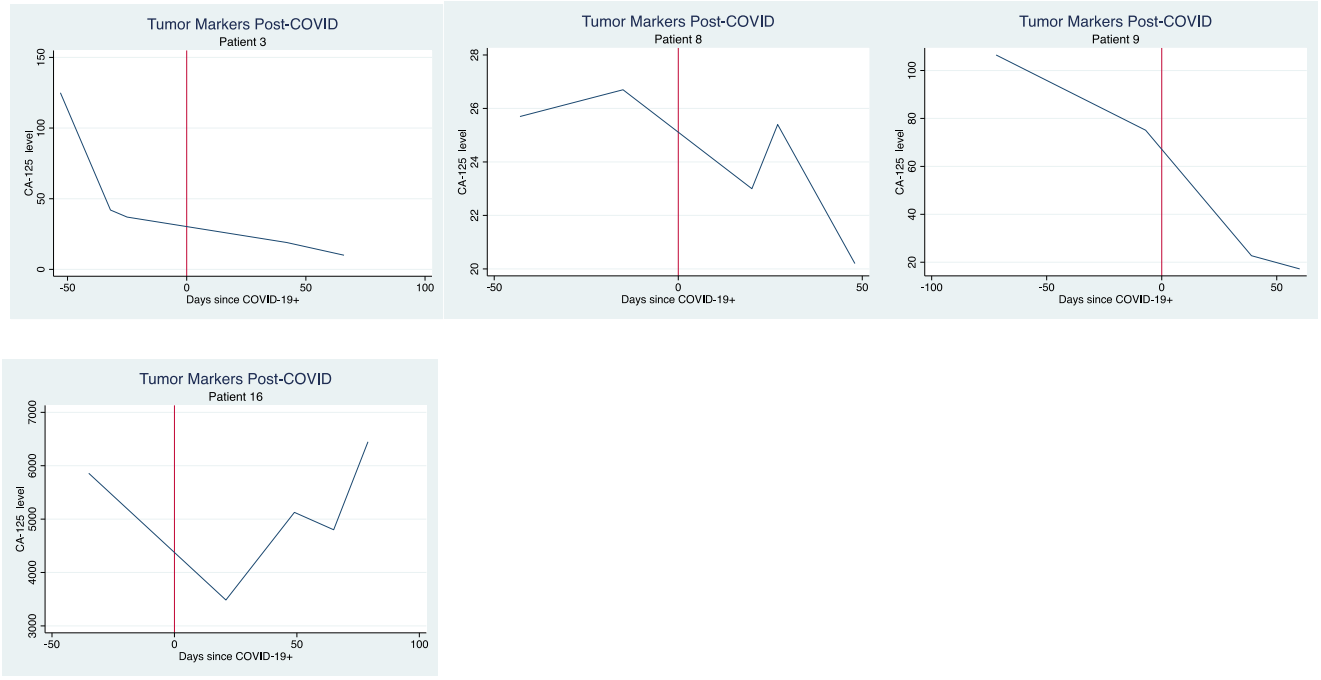


**Fig. 3.** Decreased CA-125 at the time of COVID-19 diagnosis.

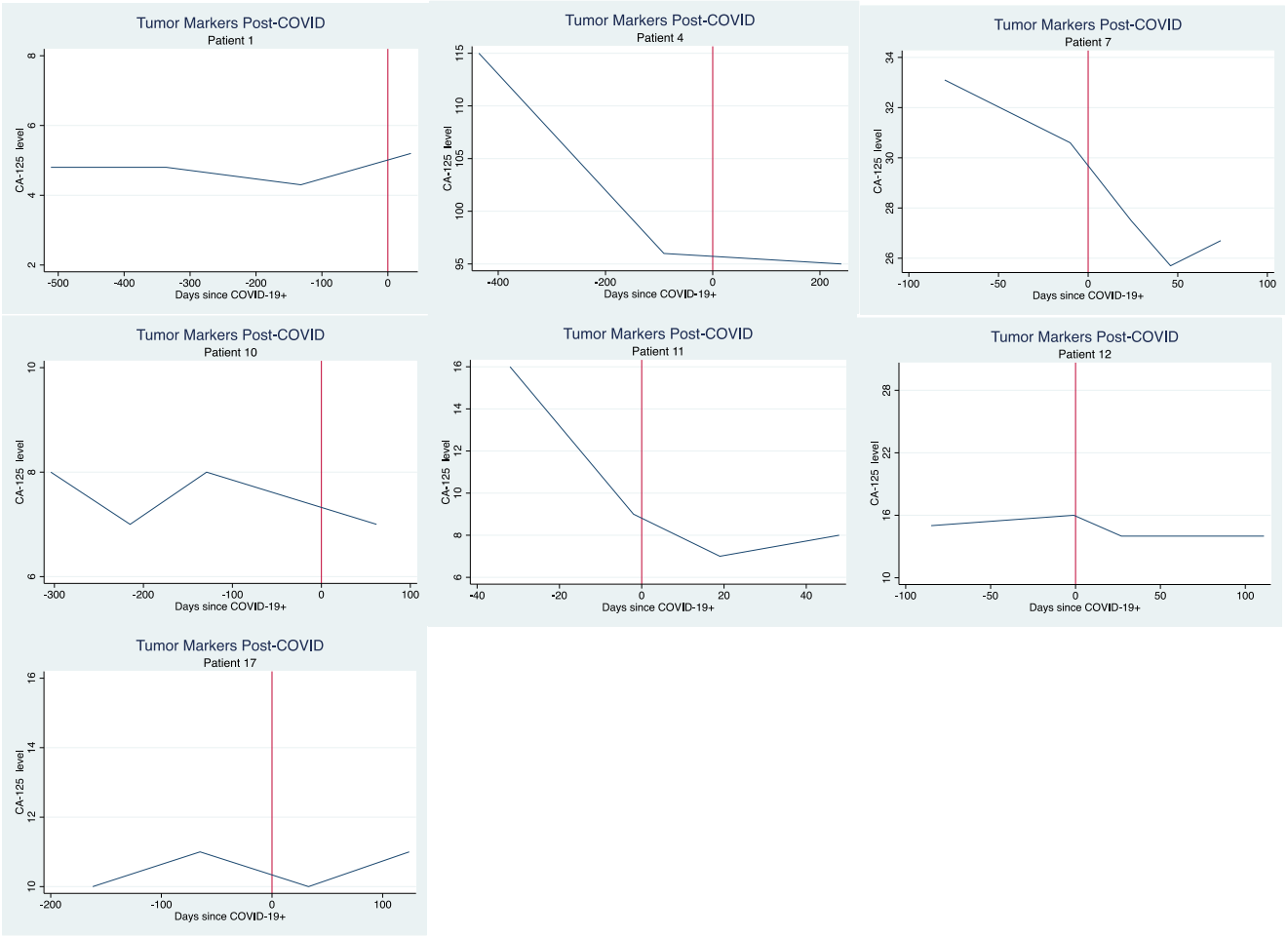


**Fig. 4.** Stable CA-125 at the time of COVID-19 diagnosis.

10.5 ± 4.6 U/mL, $p < 0.001$). While these results were statistically significant, the absolute difference in CA-125 values between these groups was small. In the context of ovarian cancer monitoring and diagnosis, the magnitude of the differences in these values may not have a clinically significant impact. Even at the upper limit of the confidence interval for the CA-125 values in the severe COVID-19 group (31.6 U/mL), the CA-125 would still be below the upper limit of normal (35 U/mL). Moreover, as Wei et al's work was done in a population of individuals without cancer, it is challenging to know the impact that COVID-19 may have on changes in CA-125 in the context of cancer. For example, ovarian cancer patients often have CA-125 values in the hundreds and thousands as illustrated by our case series. If COVID-19 were to cause a rise of 8–10 U/mL in this context, this variation may not signal concern for disease progression. However, in the case report published by Smith et al in June of 2020, they suggested that CA-125 could potentially show an increase that mimicked ovarian cancer progression. Overall, our data does not support this claim.

While some patients did show an increase in their CA-125 level coinciding with COVID-19 infection, most did not. For those who had a rise in their CA-125 trend following COVID-19 (Patients 2, 5 and 14, Fig. 1) and those who had newly documented elevated CA-125 values at the time of their COVID-19 diagnosis (Patients 6, 13 and 15, Fig. 2), all had significant cancer diagnoses that could explain their elevated CA-125 values. Many of the symptoms of COVID-19, such as hypercoagulability and shortness of breath, can mimic symptoms of cancer. Patients 6, 13 and 15 all had documentation attributing some of their symptoms to COVID-19 that were later found to also be associated with the patient's new cancer diagnosis. Importantly, patients 5 and 14 both had no evidence of recurrent disease when their CA-125 was first elevated following their COVID-19 diagnosis, but further monitoring and imaging showed that they did have a clinically significant cancer recurrence. While COVID-19 may have played a partial role in elevating some of these CA-125 readings, none could be attributed to COVID-19 alone. Certainly, additional data is needed to draw more definitive conclusions regarding CA-125 level fluctuations in the context of a COVID-19 infection, but given this information, patients with elevated CA-125 values in the context of COVID-19 should be treated as possible new cancer, cancer progression or cancer recurrence until proven otherwise.

An area of strength of our case series is that it shows a greater number of patients with CA-125 trends and COVID-19 infections in cases of gynecologic cancers. Given the importance of monitoring CA-125 in gynecologic cancer patients, we believe that this information can aid clinical decision-making. However, our cohort is still very limited. Additionally, we did not have sufficient information to categorize our patients according to the severity of their COVID-19 infection as they did in the Wei et al study. Variable information regarding COVID-19 infectious symptoms was described in patient documentation. Available details were reported in the results above, but documentation was not consistent enough to allow for stratification of patients based on severity. The CA-125 values were also drawn at varying intervals in relation to their COVID-19 diagnosis, and it is unclear how long the inflammatory effects of COVID-19 affect cancer patients. Finally, with the aim of providing rapid results, we allowed for differential follow-up in our inclusion criteria. Any patient with a CA-125 level documented after their positive COVID-19 test as of September 15, 2021 was included. This allowed patients to have anywhere between 91 and 524 days to have a CA-125 level recorded. In the end, as with any unclear clinical scenario, a thorough workup should accompany any unexplained rise in CA-125 particularly during periods of COVID-19 infections. It is possible that COVID-19 may affect the CA-125 level, but a thorough workup for cancer progression and close monitoring is still warranted. Further, prospective studies are necessary to control for these weaknesses and substantiate the results we saw in our case series.

### *CRediT authorship contribution statement*

**Susan M. Folsom:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Brigid Mumford:** Conceptualization, Investigation, Visualization, Writing – review & editing. **Lara Lemon:** Formal analysis, Methodology, Investigation, Resources, Data curation, Writing – review & editing. **Sarah Taylor:** Conceptualization, Methodology, Resources, Investigation, Resources, Supervision, 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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