Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Inflammatory markers in gynecologic oncology patients hospitalized with COVID-19 infection

Maria Smith [a], Olivia D. Lara [a], Roisin O'Cearbhaill [b,c], Anne Knisely [d], Jennifer McEachron [e], Lisa Gabor [f], Caitlin Carr [g], Stephanie Blank [g], Monica Prasad-Hayes [g], Melissa Frey [h], Justin Jee [b], Julia Fehniger [a], Yuyan Wang [i], Yi-chun Lee [e], Sara Isani [f], Jason D. Wright [d], Bhavana Pothuri [a,*]

[a] Department of Obstetrics and Gynecology, NYU Langone Health, New York, NY, United States of America
[b] Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, United States of America
[c] Weill Cornell Medical College, New York, NY, United States of America
[d] Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, New York, NY, United States of America
[e] Department of Obstetrics and Gynecology, State University of New York Downstate Medical Center, Brooklyn, NY, United States of America
[f] Department of Obstetrics & Gynecology and Women's Health, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY, United States of America
[g] Department of Obstetrics, Gynecologic and Reproductive Science, Division of Gynecologic Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America
[h] Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY, United States of America
[i] Department of Population Health, NYU Langone Health, New York, NY, United States of America

HIGHLIGHTS

- Ferritin, procalcitonin, and CRP may have prognostic value for severe COVID-19 infection in gynecologic cancer patients.
- Elevated admission white blood cell count, lactate, and creatinine may also be prognostic of severe COVID-19 disease.
- D-dimer levels do not appear to be predictive of severe COVID-19 infection in patients with gynecologic cancer.

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ABSTRACT

Objective. Elevated inflammatory markers are predictive of COVID-19 infection severity and mortality. It is unclear if these markers are associated with severe infection in patients with cancer due to underlying tumor related inflammation. We sought to further understand the inflammatory response related to COVID-19 infection in patients with gynecologic cancer.

Methods. Patients with a history of gynecologic cancer hospitalized for COVID-19 infection with available laboratory data were identified. Admission laboratory values and clinical outcomes were abstracted from electronic medical records. Severe infection was defined as infection requiring ICU admission, mechanical ventilation, or resulting in death.

Results. 86 patients with gynecologic cancer were hospitalized with COVID-19 infection with a median age of 68.5 years (interquartile range (IQR), 59.0–74.8). Of the 86 patients, 29 (33.7%) patients required ICU admission and 25 (29.1%) patients died of COVID-19 complications. Fifty (58.1%) patients had active cancer and 36 (41.9%) were in remission. Patients with severe infection had significantly higher ferritin (median 1163.0 vs 624.0 ng/mL, $p < 0.01$), procalcitonin (median 0.8 vs 0.2 ng/mL, $p < 0.01$), and C-reactive protein (median 142.0 vs 62.3 mg/L, $p = 0.02$) levels compared to those with moderate infection. White blood cell count, lactate, and creatinine were also associated with severe infection. D-dimer levels were not significantly associated with severe infection ($p = 0.20$).

Conclusions. The inflammatory markers ferritin, procalcitonin, and CRP were associated with COVID-19 severity in gynecologic cancer patients and may be used as prognostic markers at the time of admission.

1. Background

As global confirmed cases of SARS-CoV-2 (COVID-19) disease surpass 32 million and many experts predict a second wave of infections

* Corresponding author at: Department of Obstetrics and Gynecology, NYU Langone Health, 240 East 38th Street, 20th floor, New York, NY 10016, United States of America.
E-mail address: bhavana.pothuri@nyulangone.org (B. Pothuri).

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[1], it is imperative to understand the interactions between COVID-19 infection and oncologic disease. Initial reports have found high COVID-19 mortality rates in patients with cancer [2,3] and have demonstrated significant variation in mortality rates among different cancer types [4]. Prospective and retrospective studies of COVID-19 mortality in the US, Canada, and UK have demonstrated COVID-19 mortality rates between 17 and 28% among patients with active malignancy [4–6]. In a prior study, the present authors noted a mortality rate of 14% among gynecologic oncology patients in New York City (NYC) [7].

In patients with COVID-19 infection, inflammatory markers including C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), and ferritin have been shown to be significantly higher in severe disease [8]. Elevated IL-6 has also been associated with increased mortality from COVID-19 [8,9]. The excessive immune response to COVID-19 triggers a cytokine storm, leading to rapid clinical deterioration, acute respiratory distress syndrome (ARDS), and multiorgan failure [10]. Ongoing clinical trials are investigating the role of both anti-inflammatory agents such as corticosteroids (NCT04344288) and immune modulating agents such as nivolumab (NCT04343144) in COVID-19 treatment.

Despite the growing understanding of the role of the immune system and inflammation in COVID-19 among the general population, it is unclear which principles can be applied to oncology patients with COVID-19 infection as cancer is known to alter inflammatory and immunologic states in the body. Systemic inflammation has been demonstrated in many cancer types and has been associated with worse survival outcomes [11,12]. Chronic inflammation can both be the cause of malignancy or the result [13]. Inflammatory conditions such as chronic pancreatitis, inflammatory bowel disease, and hepatitis are all associated with increased risk of malignancy in the inflamed tissue [14–16]. Alternatively, tumor cells and the tumor microenvironment can express cytokines and other signaling molecules of the innate immune system throughout growth, invasion, and metastasis [13]. Chronic inflammation may lead to an immunosuppressed environment via a compensatory activation of immune suppressor cells [17]. Patients with diminished tumor-directed immune response have been found to have worse prognosis compared to those with a robust immune response [12,18]. Anti-cancer treatments can also contribute to systemic immunodeficiencies in oncology patients [19].

Although inflammatory markers in COVID-19 infection are predictive of disease severity and mortality in the general population, given the changes in systemic inflammatory and immune responses in cancer patients, it is unclear if these markers are associated with severe disease in patients with malignancy. Our aim was to describe inflammatory responses related to COVID-19 infection in patients with a history of or active gynecologic cancer to identify if inflammatory markers can be used as prognostic tools in this patient population.

2. Methods

2.1. Patients

This multi-center retrospective study identified patients from eight hospital systems in NYC with known history of gynecologic cancer who were hospitalized for COVID-19 infection between March 1, 2020 and May 30, 2020 and had available inflammatory markers data on admission. Patients were considered to have COVID-19 infection if they had laboratory-confirmed diagnosis, imaging-based diagnosis (including chest radiography or chest computed tomography), or if there was a high clinical suspicion for COVID-19 and they were treated based on COVID-19 hospital protocols. This study was approved by Institutional Review Boards at all participating sites.

2.2. Data collection

Patient data was accessed from the electronic medical record at each of the participating centers and was stored in Research Electronic Data Capture software (REDCap, Vanderbilt University) [20]. Abstracted data included patient demographics, COVID-19 severity (severe vs moderate), COVID-19 outcome (death vs recovered), cancer type, cancer stage, and cancer treatment. Severe disease was defined as COVID-19 infection requiring ICU admission, mechanical ventilation or death due to COVID-19 infection. Moderate disease was defined as COVID-19 infection requiring hospitalization but not requiring ICU admission, mechanical ventilation or resulting in death. For each patient, the following laboratory test values at the time of admission were collected: white blood cell count, absolute neutrophil count, lymphocyte count, hemoglobin, platelets, aspartate aminotransferase, alanine aminotransferase, lactate, lactate dehydrogenase, serum creatinine, troponin, total bilirubin, ferritin, D-dimer, procalcitonin, and C-reactive protein.

2.3. Statistical analysis

Patient categorical data was summarized using frequencies and percentages and continuous variables were summarized as medians (interquartile ranges). The Shapiro-Wilk test was utilized to assess for normality. The *t*-test and Wilcoxon rank-sum test was used to compare continuous variables, and categorical variables were compared using Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.0.2.

3. Results

A total of 181 patients were identified with gynecologic cancer and COVID-19 infection. There were 99 (54.7%) patients hospitalized for moderate or severe infections, and of admitted patients 86 (86.9%) had available laboratory data and were included in the analysis. Patient demographic and cancer characteristics are described in Table 1. The median age of admitted patients was 68.5 years (interquartile range (IQR), 59.0 to 74.8 years) and the distribution of gynecologic malignancies were as follows: uterine cancer, 44 (51.2%); ovarian cancer, 26 (30.2%); cervical cancer, 12 (14.0%); vulvar cancer, 1 (1.2%); vaginal cancer, 1 (1.2%); and other gynecologic cancer types, 2 (2.3%). There were 50 (58.1%) with active cancer and 36 (41.9%) patients in remission. Thirty-nine (45.3%) patients were undergoing active cancer treatment at the time of COVID-19 diagnosis, and of these patients cancer treatment included: cytotoxic chemotherapy, 23 (59.0%); endocrine therapy, 5 (12.8%); cancer directed surgery within 30 days prior to COVID-19 diagnosis, 4 (10.3%); immunotherapy, 4 (10.3%); targeted therapy, 4 (10.3%); and radiotherapy, 3 (7.7%). Smoking history was associated with COVID-19 severity ($p < 0.05$); however, 3 or more comorbidities, cancer status (remission or evidence of disease), and current cancer treatment (yes or no) were not found to be associated with COVID-19 severity.

Of the 86 patients, 29 (33.7%) patients had severe COVID-19 infection and 25 (29.1%) patients died of COVID-19 complications. Admission lab values were compared between moderate and severe groups, as shown in Table 2. Patients with severe infection had significantly higher ferritin (median 1163.0 ng/mL, IQR 640.0–1967.0 vs median 624.0 ng/mL, IQR 269.7–954.0; $p < 0.01$), procalcitonin (median 0.8 ng/mL, IQR 0.2–5.1 vs median 0.2, IQR 0.1–0.3; $p < 0.01$), and CRP (median 142.0 mg/L, IQR 62.4–217.1 vs median 62.3 mg/L, IQR 13.0–159.1; $p = 0.02$) compared to those with moderate infection. White blood cell count, lactate, and creatinine were also associated with severe disease. D-dimer levels were not significantly higher in patients with severe COVID-19 infection compared to those with moderate infection (median 10.7 μg/L, IQR 3.1–424.5 vs median 3.0 μg/L, IQR 1.0–400.0, $p = 0.20$).

Laboratory values were also compared between patients with active cancer and those in remission (Table 3). Hemoglobin was significantly lower in patients with active cancer (median 10.2 g/dL, IQR 8.4–11.9) compared to those in remission (median 12.1 g/dL, IQR 10.4–13.4,

Table 1
Patient characteristics.

Characteristic	All patients ($N = 86$)	Moderate ($N = 57$)	Severe ($N = 29$)	*P*-value
Age — median (IQR)	68.5 (59.0–74.8)	68.0 (57.0–74.0)	69.0 (63.0–77.0)	0.20
Race — *N* (%)				0.48
Caucasian	38 (44.2)	23 (40.4)	15 (51.7)	
Black	39 (45.3)	26 (45.6)	13 (44.8)	
Asian	1 (1.2)	1 (1.8)	0 (0.0)	
Other/Unknown	8 (9.3)	7 (12.3)	1 (3.4)	
Hispanic ethnicity — N (%)	13 (15.1)	7 (12.3)	6 (20.7)	0.48
Smoking history — N (%)				0.05
Never	58 (67.4)	43 (75.4)	15 (51.7)	
Former/Current	28 (32.6)	14 (24.6)	14 (48.3)	
Number of comorbidities — *N* (%)				0.77
< 3	36 (41.9)	25 (43.9)	11 (37.9)	
≥ 3	50 (58.1)	32 (56.1)	18 (62.1)	
Cancer type — N (%)				0.53
Ovary	26 (30.2)	16 (28.1)	10 (34.5)	
Uterine	44 (51.2)	28 (49.1)	16 (55.2)	
Cervical	12 (14)	9 (15.8)	3 (10.3)	
Other	4 (4.7)	4 (7.0)	0 (0.0)	
Cancer stage — N (%)				0.55
I/II	32 (37.2)	20 (35.1)	12 (41.4)	
III/IV	40 (46.5)	26 (45.6)	14 (48.3)	
Unknown	14 (16.3)	11 (19.3)	3 (10.3)	
Cancer status — N (%)				0.77
Remission	36 (41.9)	25 (43.9)	11 (37.9)	
Evidence of disease	50 (58.1)	32 (56.1)	18 (62.1)	
Current cancer treatment — N (%)				0.77
Yes	39 (45.3)	27 (47.4)	12 (41.4)	
No	47 (54.7)	30 (52.6)	17 (58.6)	
Death due to COVID-19 — N (%)	25 (29.1)	0 (0.0)	25 (86.2)	NA

Table 3
Laboratory data in active cancer vs remission groups.

Laboratory data- median (IQR)	Active Cancer ($N = 50$)	Remission ($N = 36$)	*P*-value
Ferritin- ng/mL	954.0 (319.0–1833.0)	517.0 (323.0–890.0)	0.08
Procalcitonin- ng/mL	0.2 (0.1–0.9)	0.2 (0.1–0.3)	0.05
C-reactive protein- mg/L	86.0 (13.4–192.7)	81.7 (33.6–183.0)	0.90
Lactate- mmol/L	1.5 (1.0–2.9)	1.5 (1.0–2.0)	0.43
Serum creatinine- mg/dL	1.0 (0.7–2.1)	1.0 (0.7–1.6)	0.92
White blood cell count- per mm^3	7.2 (4.0–12.8)	6.6 (5.1–10.6)	0.69
Absolute neutrophil count- per mm^3	5.6 (2.9–10.1)	5.4 (3.5–9.0)	0.90
Lymphocyte count- per mm^3	0.8 (0.5–1.2)	0.9 (0.6–1.1)	0.51
Hemoglobin- g/dL	10.2 (8.4–11.9)	12.1 (10.4–13.4)	<0.01
Platelets- per mm^3	272.5 (160.5–437.2)	215.0 (174.0–281.5)	0.15
D-dimer- μg/L	11.4 (2.3–447.0)	2.3 (0.7–355.0)	0.07
Aspartate aminotransferase- U/L	34.0 (25.0–54.8)	42.0 (27.0–58.0)	0.38
Alanine aminotransferase- U/L	25.0 (12.8–38.0)	28.0 (19.0–49.8)	0.12
Lactate dehydrogenase- U/L	377.0 (310.0–515.0)	361.0 (320.0–446.5)	0.65
Troponin- ng/mL	0.03 (0.01–0.1)	0.02 (0.01–0.03)	0.48
Total bilirubin- mg/dL	0.4 (0.3–0.7)	0.5 (0.4–0.8)	0.10

$p < 0.01$). No other laboratory values were found to be significantly different between active cancer and remission groups. Ferritin, D-dimer, and procalcitonin trended towards higher levels in those with active cancer (median 954.0 μg/mL, IQR 319.0–1833.0; median 11.4 μg/L, IQR 2.3–447.0; median 0.2 ng/mL IQR 0.1–0.9 respectively) compared to those in remission but were not significantly different (median 517.0 μg/mL, IQR 323.0–890.0, $p = 0.08$; median 2.3 μg/L, IQR 0.7–355.0, $p = 0.07$; median 0.2, IQR 0.1–0.3, $p > 0.05$ respectively).

4. Discussion

This multi-center study of gynecologic cancer patients hospitalized for COVID-19 infection found that the inflammatory markers ferritin, procalcitonin, and C-reactive protein were significantly higher at the time of admission in patients who went on to develop severe infection requiring ICU admission, mechanical ventilation, or resulting in death. Higher white blood cell count, creatinine, and lactate were also associated with severe COVID-19 infection. These findings in patients with a known history of gynecologic cancer are consistent with prior studies of inflammatory, hematologic, and coagulation markers in COVID-19 infection. Two independent meta-analyses of inflammatory markers in COVID-19 infection among the general population have reported significantly higher inflammatory markers in patients with severe COVID-19 and COVID-19 mortality, including CRP, ESR, ferritin, procalcitonin, and IL-6 [9,21,22]. One meta-analysis also found significant associations between hematologic markers and COVID-19 severity and death, including WBC and D-dimer. Furthermore, when admission inflammatory markers between patients with active gynecologic cancer and in remission were compared, except for a decrease of hemoglobin in patients with active cancer, no differences in laboratory values between patients with active cancer and those in remission were noted. A significant decrease in hemoglobin in patients with active cancers can be attributed to a variety of reasons including vaginal bleeding associated with gynecologic malignancy, anemia of chronic disease, or chemotherapy induced anemia [23–25].

Table 2
Laboratory data at hospital admission in patients with severe vs. non-severe COVID-19 infection.

Laboratory data- median (IQR)	All patients ($N = 86$)	Moderate ($N = 57$)	Severe ($N = 29$)	*P*-value
Ferritin- ng/mL	673.0 (320.0–1627.0)	624.0 (269.7–954.0)	1163.0 (640.0–1967.0)	<0.01
Procalcitonin- ng/mL	0.2 (0.1–0.7)	0.2 (0.1–0.3)	0.8 (0.2–5.1)	<0.01
C-reactive protein- mg/L	83.0 (13.9–189.0)	62.3 (13.0–159.1)	142.0 (62.4–217.1)	0.02
Lactate- mmol/L	1.5 (1.0–2.6)	1.1 (1.0–1.8)	2.2 (1.5–5.3)	<0.01
Serum creatinine- mg/dL	1.0 (0.7–1.8)	0.8 (0.7–1.2)	1.7 (1.0–2.5)	<0.01
White blood cell count- per mm^3	6.9 (4.4–12.1)	6.6 (4.2–10.1)	11.0 (5.9–15.8)	0.02
Absolute neutrophil count- per mm^3	5.4 (3.2–9.9)	5.1 (3.0–7.9)	8.8 (3.7–13.9)	0.07
Lymphocyte count- per mm^3	0.8 (0.6–1.1)	0.9 (0.6–1.2)	0.8 (0.5–1.1)	0.50
Hemoglobin- g/dL	10.8 (9.0–12.8)	11.2 (8.7–12.9)	10.6 (9.2–11.7)	0.23
Platelets- per mm^3	236.0 (173.0–347.0)	241.0 (174.0–319.0)	231.0 (168.3–347.8)	0.90
D-dimer- μg/L	5.6 (1.3–423.5)	3.0 (1.0–400.0)	10.7 (3.1–424.5)	0.20
Aspartate aminotransferase- U/L	37.0 (25.0–56.5)	34.0 (24.5–55.0)	44.0 (28.5–83.5)	0.17
Alanine aminotransferase- U/L	26.0 (16.3–43.3)	25.0 (17.0–38.0)	28.0 (15.0–56.0)	0.63
Lactate dehydrogenase- U/L	371.0 (310.8–470.3)	347.0 (308.0–453.8)	412.0 (336.0–600.3)	0.08
Troponin- ng/mL	0.03 (0.01–0.1)	0.02 (0.01–0.08)	0.03 (0.02–0.1)	0.45
Total bilirubin- mg/dL	0.5 (0.3–0.7)	0.4 (0.3–0.7)	0.5 (0.4–0.8)	0.47

As acute phase reactants, inflammatory markers such as ferritin and CRP are non-specific markers of inflammation and can be elevated in both patients with cancer and active infection [26]. Ferritin binds iron intracellularly and is an indirect marker of total body iron stores [27] and during infection its role is to sequester iron and prevent its uptake by microbes [28]. CRP is secreted by hepatocytes in response to IL-6 secreted by macrophages and works to opsonize microbes and necrotic or apoptotic cells so they can be phagocytosed [29]. Procalcitonin is typically thought to be elevated in bacterial, fungal, and protozoal infections rather than viral infections [30]. In COVID-19 infection, however, one meta-analysis demonstrated increased procalcitonin levels were associated with a five-fold higher risk of developing severe COVID-19 infection in the general population [31]. The use of procalcitonin levels as a marker for infection has been controversial in cancer patients. Studies have demonstrated that patients with solid tumors have higher baseline procalcitonin than patients in remission or without a history of cancer, and patients with more advanced cancer have higher procalcitonin than those with early-stage disease [32,33]. In this cohort, despite finding a non-significant elevation of these inflammatory markers in patients with active cancer compared to remission, ferritin, procalcitonin, and CRP at hospital admission still had prognostic value in predicting the severity of COVID-19 infection.

No significant difference in D-dimer levels between moderate and severe COVID-19 infections were identified in these data. One study of D-dimer levels in hospitalized patients with COVID-19 determined D-dimer greater than 2000 μg/L was predictive of in-hospital mortality with a sensitivity of 92.3% and a specificity of 83.3% [34]. In our study c there was considerable variability in D-dimer levels which ranged from 0.3–4768.0 μg/L. Baseline elevation in D-dimer levels due to a hypercoagulable state in cancer patients may confound the effect of COVID-19 infection on D-dimer levels and blunt the predictive powers of this test in patients with malignancy [35].

This study has several limitations. First, it was a retrospective study, which may have resulted in selection bias. This study also lacked a control group of patients with gynecologic cancer without COVID-19 infection for comparison of laboratory values. Additionally, for 13 of the 99 hospitalized patients followed for gynecologic malignancy at participating centers, laboratory data was not accessible due to a COVID-19 admission at an outside hospital. These patients were excluded from analysis. Five of the 13 excluded patients had moderate COVID-19 illness and 8 had severe COVID-19 infections, therefore a relatively higher proportion of patients with severe infections were excluded which may have added additional bias to our results. In addition, this dataset is limited by the number of COVID-19 infections in gynecologic cancer patients in NYC. Replicating these data with a larger cohort will be important, particularly with respect to D-dimer. Finally, as this study took place at institutions in NYC during the initial surge, it is unclear if the results are generalizable to patients outside of NYC.

In conclusion, the present study demonstrated that elevated ferritin, procalcitonin, C-reactive protein, white blood cell count, creatinine, and lactate at the time of admission in patients with gynecologic cancer hospitalized with COVID-19 infection may be used as prognostic markers for severe disease. D-dimer does not appear to be a marker of disease severity in gynecologic oncology patients with COVID-19 infection. Further studies are warranted to confirm these findings. This information will be valuable in understanding the prognostic significance of inflammatory markers and counseling gynecologic cancer patients who are hospitalized with COVID-19 as the pandemic continues or re-surges.

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Author contributions

M.S., O.D.L., and B.P. contributed to the study design, acquired and analyzed data and wrote the manuscript. M.S. and Y.W. contributed to statistical analysis. R.OC., A.K., J.M., L.G., J.J., J.F., Y.L. C.C., S.B., M.P.H., and M.F., contributed to data acquisition. R.OC, J.W. and S.I. provided intellectual input. All authors contributed to the interpretation of data, vouched for the data analysis, contributed to the editing of the manuscript, and agreed to publication of this study.

Declaration of Competing Interest

Maria Smith, Olivia D. Lara, Anne Knisely, Jennifer McEachron, Lisa Gabor, Caitlin Carr, Stephanie Blank, Monica Prasad-Hayes, Melissa Frey, Julia Fehniger, Yi-chun Lee, Sara Isani, and Yuyan Wang have nothing to disclose. Roisin O'Cearbhaill reports personal fees from Tesaro, personal fees from Glaxosmithkline, personal fees from Regeneron, other from Genentech USA, outside the submitted work; and Non-compensated steering committee member for the PRIMA, Moonstone (Tesaro/GSK) and DUO-O (AstraZeneca) studies. Justin Jee reports a patent 16/686,663, 2020 licensed to MDSeq Inc. Jason D. Wright receives research funding from Merck and is a consultant for Clovis Oncology. Bhavana Pothuri reports grants, personal fees and non-financial support outside the submitted work; institutional PI for industry sponsored trials from Tesaro/GSK, AstraZeneca, Merck, Genentech/ Roche, and Clovis Oncology. Compensated advisory boards include Tesaro/GSK, AstraZeneca, Merck, Mersana and Eisai.

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