Cytomegalovirus and systemic inflammation at time of surgery is associated with worse outcomes in serous ovarian cancer

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H I G H L I G H T S

- Women previously exposure to cytomegalovirus and high C-reactive protein have worse RFS and OS vs. not previously exposed.
- CMV+ but CRP- had the longest OS, indicating CMV exposure, in the absence of inflammation, may have protective properties.
- Inflammation and CMV serostatus at the time of surgery appear to impact survival and may influence the immune response.

A R T I C L E   I N F O

A B S T R A C T

Objectives: Cytomegalovirus (CMV) is a common infection that establishes latency in healthy people. CMV has been associated with alterations of the immune compartment leading to improved responses, while inflammation has been shown to adversely impact outcomes. We investigated whether CMV serostatus predicts outcomes in ovarian cancer in the presence or absence of inflammation.

Methods: A total of 106 patients with serous ovarian cancer from 2006 to 2009 were analyzed. CMV and systemic inflammation was measured using CMV immunoglobulin G (IgG) and C-reactive protein (CRP), respectively, in serum collected prior to cytoreduction. Patients were stratified by CMV IgG (non-reactive, reactive/borderline) and CRP ($\leq$10, >10 mg/L) status. Overall survival (OS) and recurrence-free survival (RFS) were compared by group using log-rank tests and Cox proportional hazards regression models adjusting for age at surgery.

Results: Of 106 eligible patients, 40 (37.7%) were CMV+/CRP+, 24 (22.6%) CMV+/CRP-, 19 (17.9%) CMV−/CRP+, and 23 (21.7%) CMV−/CRP−. CRP+ had higher CA-125 levels ($P = 0.05$) and higher rates of suboptimal debulking ($P = 0.03$). There were no other significant differences in demographic, surgical, or pathologic factors between groups. CMV+/CRP+ patients median RFS and OS were 16.9 months (95% CI: 9.0–21.1) and 31.7 months (95% CI: 25.0–48.7), respectively, with a significantly worse RFS (aHR: 1.85, 95% CI: 1.05–3.24, $P = 0.03$) and OS (aHR: 2.12, 95% CI: 1.17–3.82, $P = 0.01$) compared to CMV−/CRP− (RFS = 31.2 months (95% CI: 16.0–56.4) and OS = 63.8 months (95% CI: 50.7–87.0)). CMV+/CRP− group displayed the longest OS (89.3 months).

Conclusions: Previous exposure to CMV and high CRP at surgery portended worse RFS and OS compared to women who tested negative. The CMV+/CRP− group had the longest OS, indicating that CMV status alone, in the absence of inflammation, may be protective.

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1. Introduction

Ovarian cancer is a heterogeneous group of malignancies with an estimated 21,750 new cases diagnosed and 13,940 disease related deaths in the United States (U.S.) for 2020 [1]. Epithelial ovarian cancers comprise approximately 90% of all cases, with serous histology being the most

common subtype. Over 80% of high-grade serous carcinomas are advanced stage (stage III or IV) at time of diagnosis, reflecting the aggressive nature of the disease [2]. The vast majority of these women treated with a combination of surgery and chemotherapy will respond and enter remission. Unfortunately, 75%–80% of patients diagnosed with high-grade serous-carcinomas will ultimately relapse, with fewer than one-half surviving beyond 5 years. New strategies in prevention, early detection, and better treatments are needed to decrease the risk of relapse.

There is a pressing need to better understand the biology and pathogenesis of serous ovarian carcinoma. The prevailing model of carcinogenesis suggests that tumors originate from precursor lesions in the fallopian tube fimbriae with early spread to ovaries and peritoneal surfaces [3]. The main molecular characteristic is marked genomic instability, reflected with high DNA copy number alterations and ubiquitous *TP53* mutations. The role of inflammatory and immunological factors in the initial development of ovarian cancer, and the subsequent risk of recurrence, is poorly understood. Novel information regarding the systemic status of the immune system in women with ovarian cancer is emerging and suggests a highly immunosuppressive environment [4].

Infectious agents, alone or in combination with chronic inflammation, can be promoters of carcinogenesis. The herpesvirus human cytomegalovirus (CMV) is a common infection that establishes latency in healthy people [5]. The seroprevalence increases gradually with age with approximately 60% of U.S. adults seropositive for CMV [6]. The virus encodes more than 750 proteins, many of which are known to interfere with immunologic functions [7]. The role of CMV is not well established in human cancer, but emerging evidence suggests that CMV may have oncomodulatory properties that play an important role across multiple types of cancers [8–12]. CMV DNAemia was found to be present in the tumor and the fallopian tube of more than two thirds of patients with epithelial ovarian cancer [13]. Studies of CMV infection suggest that it may promote transformation and cause a more rapid development of cancer through eliciting inflammation and leukocyte dysfunction [13]. In another study, ovarian tissues from women undergoing surgery for suspected ovarian pathology were evaluated for CMV DNA. The authors found that 50% of cases with detectable CMV DNA in their tissues had ovarian cancer, while none of the benign ovaries were positive for CMV DNA [14]. These findings suggest that CMV could be playing a role in altering the tumor microenvironment (TME) or inducing inflammation, which may promote the invasive potential of ovarian cancer. CMV was also found to be present in up to 80% of pre-chemotherapy ovarian cancer tissue samples, which was reduced to 44% after chemotherapy [15]. In that study, patients with CMV positive tumors had shorter median overall survival rates suggesting a relationship may exist between CMV infection and the development and progression of epithelial ovarian cancer.

Inflammation is considered an important factor in carcinogenesis. One measure of inflammation is C-reactive protein (CRP), which is an important acute phase reactant (APR) protein that is released by hepatocytes in response to tissue injury and inflammation [16,17]. Changes in levels of APR proteins result largely from the effects of cytokines, particularly interleukin (IL)-6, as well as IL-1 beta, tumor necrosis factor (TNF)-alpha, and interferon gamma [18–20]. CRP has been linked to both pro-inflammatory and anti-inflammatory actions [16]. Previously, circulating CRP has been used as a marker for various acute and chronic inflammatory diseases [21]. CRP concentrations >1 mg/dL (10 mg/L) are commonly thought to indicate clinically significant inflammation while concentrations between 0.3 and 1 mg/dL (3 and 10 mg/L) indicate what is commonly referred to as low-grade inflammation [22]. Moderate to high levels of CRP have been associated with cancer [17]. In one study, women with CRP concentrations >10 mg/L, compared to <1 mg/L, were at significantly increased risk of ovarian cancer (OR = 1.67, 95% CI = 1.12, 2.48) [17]. In addition, higher levels of CRP have been associated with decreased overall survival possibly due to the promotion of carcinogenesis by damaging DNA, stimulating angiogenesis, cell proliferation, and inhibiting apoptosis [16,17].

The interaction between CMV and CRP may also alter the ability of certain immune cells to induce a potent anti-tumor response. In a previous study, CRP was shown to suppress the anti-tumor response of T cells [23]. Studies evaluating the contribution of CMV in cancer have identified a subset of natural killer (NK) cells, adaptive NK cells, that are long-lived and display enhanced activity [24–26]. Based on these studies, the various settings of inflammation and previous CMV exposure in ovarian cancer may alter the NK and T cell response leading to changes in patient outcomes.

The current study aimed to investigate the role of CMV serostatus at the time of surgery, segregating patients by high vs. low inflammation, on outcomes in women with high-grade serous ovarian cancer. To accomplish this, we conducted a retrospective cohort study among women with high-grade serous ovarian cancer who underwent cytoreductive surgery at the University of Minnesota between 2006 and 2009 and had a blood sample collected at the time of surgery.

2. Methods

2.1. Patients and eligibility

Following approval by the University of Minnesota Institutional Review Board, a registry of biobanked specimens maintained at the University of Minnesota was queried for pathological diagnosis of serous ovarian cancers from 2006 through 2009. Inclusion criteria included individuals aged 18 or older, treated at the University of Minnesota between 2006 and 2009 who had a pathologic diagnosis of serous ovarian cancer and an available blood sample from time of surgery. Exclusion criteria included cancer other than high-grade (2 or 3) serous histology, lack of blood specimen with primary or interval cytoreductive surgery, and individuals who only received surgical treatment at the University of Minnesota and had no follow-up clinical data. A total of 149 patients were identified, with 106 patients ultimately eligible for this analysis. Patients were not eligible due to lack of blood specimen (n = 14), benign histology (n = 10), cancer other than high-grade serous ovarian cancer (n = 8), specimens associated with secondary surgeries (n = 6), and incomplete (n = 4) or duplicate (n = 1) medical records (Fig. 1).

Medical records were reviewed and the following demographic, surgical, and pathological variables collected: date of birth, date of initial diagnosis, race, ethnicity, body mass index (BMI), primary surgical procedures, debulking status (no evidence of disease/optimal, suboptimal, or unknown), histology, tumor grade (1, 2, or 3), stage, primary treatment, initial cancer antigen 125 (CA 125) level, diagnosis and date of recurrence, date of death, date of last follow-up.

Recurrence free survival (RFS) was measured by time in months from the date of initial diagnosis to the date of first sign of cancer recurrence (elevation in CA 125 or image confirmation of tumor recurrence) or death, or censored at date of last follow-up if recurrence free and alive. Overall survival (OS) was measured as the time in months from the date of initial diagnosis to the date of death, or censored at date of last follow-up if still alive. Date and cause of death were obtained from the medical record and supplemented with data from the Minnesota Department of Health. Both RFS and OS were censored at 10 years.

2.2. Serum samples

The University of Minnesota Tissue Procurement Facility staff collected blood samples from individuals in the preoperative period with diagnosis or suspected ovarian malignancy following receipt of written informed consent. Samples were processed by standard operating procedures, divided into aliquots, and stored at −80 °C [27].

CMV IgG serostatus was measured with an FDA approved CMV IgG reagent/sandwich immunoassay on a Roche Cobas e411 analyzer (Roche Diagnostics) at a CLIA certified laboratory. Results were interpreted as reactive, non-reactive, or borderline according to their
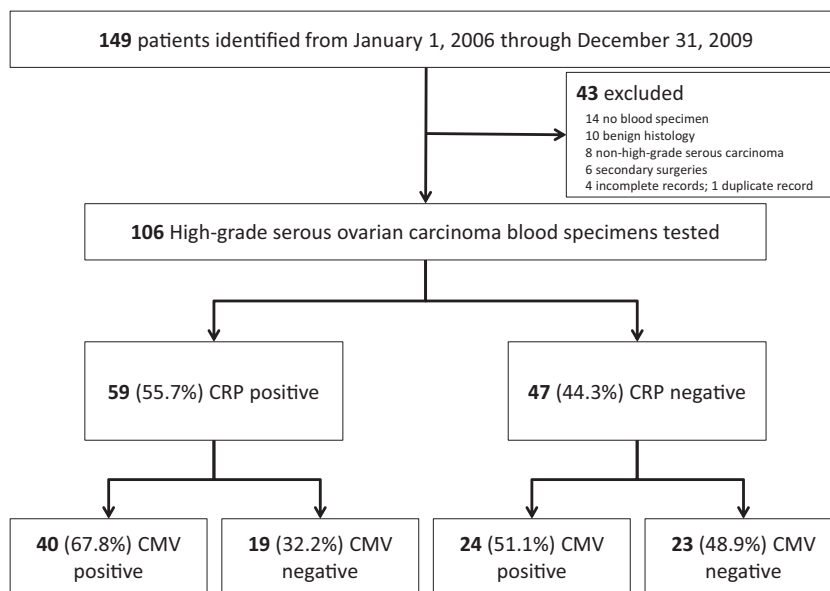
Fig. 1. Flow diagram showing patients included in the study. Schema of experimental design with stratification into four groups.

standards. For our analysis, CMV borderline ($n = 7$) results were combined with CMV reactive. CMV+ in this study refers to serostatus and presence of antibodies against CMV and not necessarily active CMV infection.

Serum CRP levels (mg/L) were measured with an FDA approved immunoturbidimetric method on a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN) at a CLIA certified laboratory. Results were interpreted as positive using levels >10 mg/L.

2.3. Statistical analysis

Patient demographic, surgical, and pathological data were summarized; means ± standard deviations (SD) and percentages are presented unless otherwise noted. Patients were categorized into four groups based on CMV status (non-reactive (−), reactive/borderline (+)) and CRP (≤10 mg/L(−), >10 mg/L(+)). Comparisons of baseline characteristics by group were conducted using Chi-Square tests and Fisher's Exact tests as appropriate for categorical variables and *t*-tests and Wilcoxon Rank-Sum tests as appropriate for continuous values. OS and RFS were summarized using Kaplan-Meier methods and compared by group using log-rank tests. Cox proportional hazards regression models were conducted to compare OS and RFS by group while also adjusting for age at surgery, a known confounding variable and decided a priori. A sensitivity analysis adjusting for variables identified as different between the groups during analysis (CA-125 and debulking status) was conducted and did not alter conclusions. Adjusted hazard ratios (aHR) and 95% confidence intervals (CI) are presented. Data were analyzed using SAS 9.4 (Cary, NC) and *P*-values less than 0.05 were considered statistically significant.

3. Results

Of the 106 women eligible for inclusion, 40 (37.7%) were CMV+/CRP+, 24 (22.6%) were CMV+/CRP−, 19 (17.9%) were CMV−/CRP+, and 23 (21.7%) were CMV−/CRP− (Fig. 1). Just over half of the women were CRP positive ($n = 59$; 55.7%). The average age of women in the study was 63.4 ± 11.1 years with an average BMI of 27.9 ± 6.6 kg/m^2 (Table 1). The vast majority of women ($n = 91$; 85.8%) had advanced-stage disease (stage III or IV) and underwent primary cytoreductive surgery ($n = 91$; 85.8%). Individuals in the high CRP (CRP+) groups had

higher initial CA 125 levels ($P = 0.05$) and higher rates of suboptimal cytoreductive surgery ($P = 0.02$; Table 1). There were no other significant differences in demographic, surgical, or pathologic factors between groups.

The median RFS was 20.6 months (95% CI: 17.8–27.1) and median OS was 54.5 months (95% CI: 46.1–61.3) for the entire cohort. Median RFS (16.9 months (95% CI: 9.0–21.1)) and OS (31.7 months (95% CI: 25.0–48.7)) was shortest for women who were CMV+/CRP+ at time of cytoreductive surgery (Fig. 2). RFS and OS in this group were significantly poorer than those in the CMV−/CRP− group (median 31.2 months (95% CI: 16.0–56.4); aHR: 1.85, 95% CI: 1.05–3.24, $P = 0.03$ and median 63.8 months (95% CI: 50.7–87.0); aHR: 2.12, 95% CI: 1.17–3.82, $P = 0.01$, respectively). The CMV+/CRP- group displayed the longest OS (89.3 months) while the CMV−/CRP− group had the longest RFS (31.2 months).

We then focused on patients who had high levels of CRP (Fig. 3). RFS was not statistically significantly different between CMV reactive or nonreactive groups (CMV+ vs. CMV− median RFS 16.9 vs. 20.6 months; aHR = 1.48, 95% CI: 0.78, 2.81, $P = 0.24$). However, among patients with high levels of CRP, those who were CMV reactive had poorer OS than those who were nonreactive (median OS 31.7 vs. 49.7 months; aHR = 2.13, 95% CI: 1.07, 4.21, $P = 0.03$).

4. Discussion

In this high grade serous ovarian cancer population, patients who tested positive for CMV IgG and had high levels of CRP at cytoreductive surgery had worse RFS and OS compared to women who tested negative for CMV. Our data suggest an additive negative effect of CMV seropositive status and elevated CRP levels on the outcome of epithelial ovarian cancer. In addition, our data showed the CMV+/CRP− group had the longest OS, suggesting that CMV status alone at the time of surgery, in the absence of inflammation, may have protective properties.

As discussed earlier, a previous study evaluating the presence of CMV in ovarian cancer tissue samples showed up to 80% of samples were positive pre-chemotherapy, but was reduced to 44% following chemotherapy [15]. The results of this study suggested a correlation between CMV infection and epithelial ovarian cancer. In another study, CMV DNA was detected in patients with ovarian cancer, but not in benign patient samples [22], further supporting the role of CMV in altering

Table 1
Patient demographic and clinicopathologic characteristics ($N = 106$).

	CMV+/CRP+		CMV+/CRP−		CMV−/CRP+		CMV−/CRP−		P-value
	N	%	N	%	N	%	N	%	
Age, years (mean ± SD)	40	65.9 ± 10.7	24	62.7 ± 13.9	19	59.7 ± 8.9	23	62.8 ± 9.9	0.23
BMI, kg/m²* (mean ± SD)	32	29.5 ± 7.8	23	27.1 ± 5.4	18	275 ± 6.9	18	26.5 ± 5.2	0.37
Race									0.57
White	31	77.5	16	66.7	15	79	19	82.6	
Other	4	10	4	16.7	1	5.3	0	0	
Unknown	5	12.5	4	16.7	3	15.8	4	17.4	
Initial CA 125** (median, range)	38	549 (8–12,654)	23	117 (11–23,152)	17	584 (32–6449)	21	325 (23–14,779)	0.05
Debulking Surgery Status									0.02
Optimal	26	65	17	70.8	12	63.2	20	87	
Suboptimal	12	30	1	4.2	5	26.3	2	8.7	
Unknown	2	5	6	25	2	10.5	1	4.4	
Grade									0.38
2	10	25	4	16.7	3	15.8	7	30.4	
3	30	75	18	75	16	84.2	16	69.6	
Unknown	0	0	2	8.3	0	0	0	0	
Stage***									0.11
I	2	5	3	12.5	1	5.3	3	13	
II	0	0	3	12.5	0	0	3	13	
III	31	77.5	16	66.7	12	63.2	13	56.5	
IV	7	17.5	2	8.3	6	31.6	4	17.4	
Primary Treatment									0.98
Neoadjuvant	5	12.5	3	12.5	2	10.5	4	17.4	
Primary surgery	34	85	21	87.5	17	89.5	19	82.6	
Unknown	1	2.5	0	0	0	0	0	0	

* body mass index.
** Cancer Antigen-125.
*** Cancer stage based on International Federation of Gynecology and Oncology (FIGO) 2014 classification.
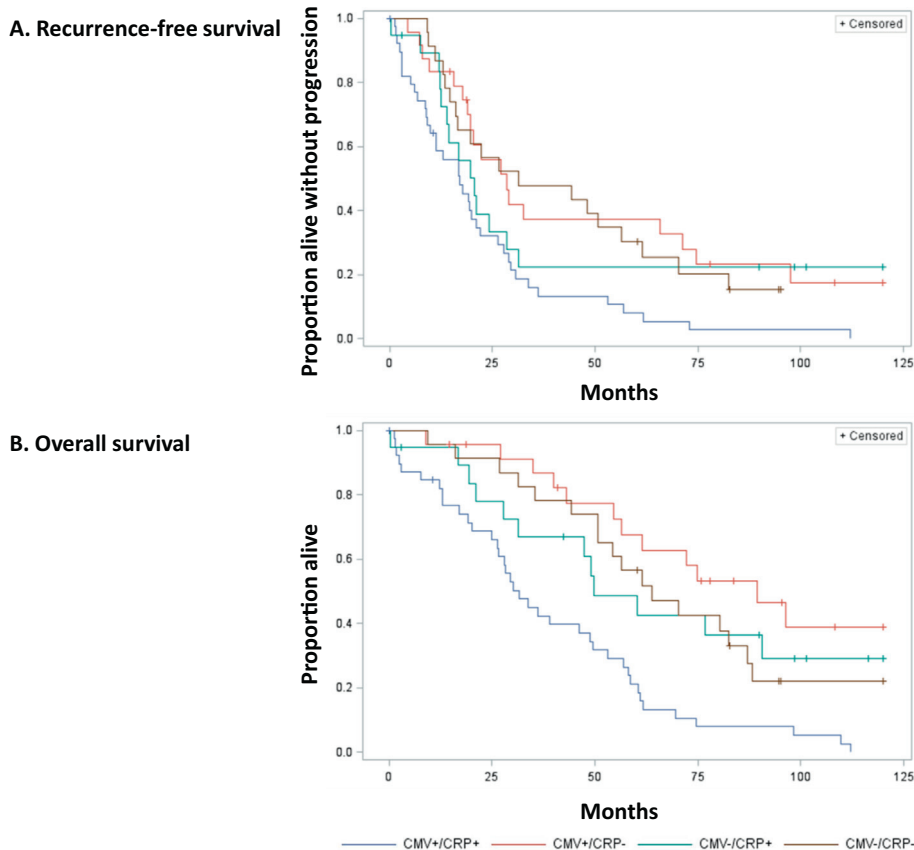

Fig. 2. Recurrence-free and overall survival for all subgroups. Kaplan-Meier curves for each of the four groups (CMV+/CRP+, CMV+/CRP−, CMV−/CPR+, CMV−/CRP-) for recurrence-free survival (Panel A) and overall survival (Panel B).
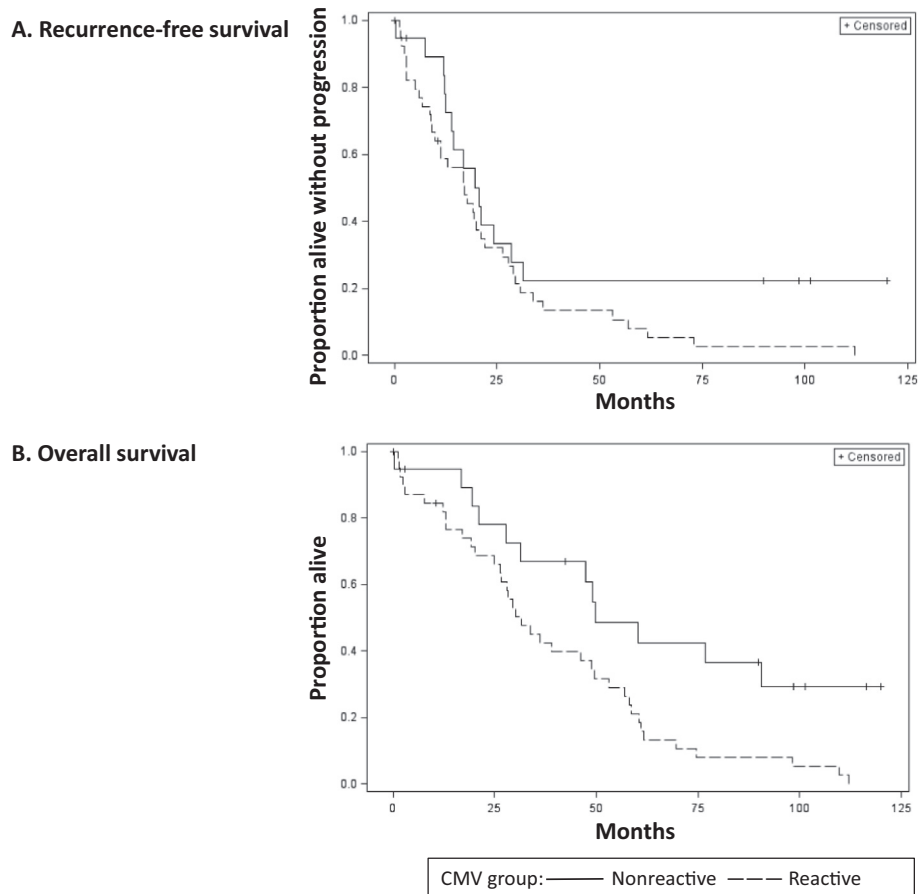
Fig. 3. Recurrence-free and overall survival for CRP positive patients. Kaplan-Meier curves of CMV+ and CMV− patients among those who are CRP positive for recurrence-free survival (Panel A) and overall survival (Panel B).

the TME to promote ovarian cancer. Our data provide additional support of CMV as a possible modulator of ovarian cancer. However, our data suggest the effects of CMV serostatus on survival may be dependent on the inflammatory response elicited at the time of surgery.

CRP has been used as a marker of inflammation and cytokine release for a variety of diseases. In ovarian cancer CRP levels have been shown to be elevated in more advanced tumor stages and elevated levels have been associated with suboptimal cytoreduction [28]. Furthermore, high circulating CRP levels have been shown to promote ovarian cancer [29] through the accumulation of cellular mutations, proliferation and metastatic spread by stimulating angiogenesis which correlate with poor outcomes [28]. Little is known whether circulating measurements of CRP truly correlate with localized inflammation, but it is possible that high circulating CRP levels (>10 mg/L) may augment localized inflammation in the ovary [17]. There is also evidence to suggest that CRP levels cycle over time in patients [30] [31], which may provide a window of opportunity where the immune response is better able to respond. However, in the context of CMV infection the environment may be altered limiting the ability of the immune system to mount a strong response, but further studies are needed to understand how CMV impacts responses in this setting.

In exploring CMV serostatus and CRP and their effects on ovarian cancer outcome, it is plausible to explore the effect of CRP on T cell responses. CRP has been shown to suppress T cell responses to tumor [23]. The T cell response to oncologic threat is a critical component of the immune response, which is driven by cytokines like IL-2 that are produced but also required by T cells. Importantly, IL-2 is responsible for the activation of natural killer (NK) cells, a component of the innate immune system, but also contributes to the generation of T-regulatory

cells. Thus increased inflammation, and associated CRP levels, may simultaneously result in induction of the innate immune response as well as immune suppressive cells, causing an overall deficit of immunologic activity against the tumor.

Another possible consideration impacting tumor response by CMV serostatus in the presence or absence of inflammation is the regulation of the adaptive natural killer (NK) cell response. NK cell maturation and function are shaped by the environment. Viral infections such as CMV have been shown to alter the function of NK cells, leading to the expansion of a diverse subset of NK cells known as adaptive NK cells [24]. In 2004, Lopez-Botet and colleagues found a unique population of NKG2C+ NK cells in CMV seropositive, but not CMV seronegative humans [32]. Other herpes viruses such as Herpes Simplex or Epstein Barr virus were not found to induce these cells. Definitive data demonstrate that NKG2C+ and NKG2C+/CD57+ NK cells expand when immunosuppressed patients reactivate CMV after solid organ or hematopoietic cell transplantation [33]. These NKG2C+ NK cells are long-lived, mediate potent antibody dependent cellular cytotoxicity (ADCC), and are capable of enhanced target cell killing and interferon ɣ production, as compared to NK cells lacking NKG2C. These findings suggest that NKG2C+ NK cells represent a unique NK cell population primed by human CMV. In a transplant setting, CMV reactivation was shown to be associated with a higher frequency and number of CD56dim/NKG2C+/CD57 adaptive NK cells [25]. This subset of NK cells demonstrated enhanced antitumor activity [25,26]. However, chronic NKG2C receptor stimulation in combination with IL-15 can induce expression of inhibitory receptors, LAG-3 and PD-1, leading to NK cell exhaustion [34]. Adaptive NK cell activity has also been shown to be restricted due to overexpression of Tim-3 on NK cells in the setting

of cancer or during persistent infection due to hepatitis B virus and HIV infections [35]. These data suggest that although CMV infection can lead to expansion of an adaptive NK cell population with enhanced cytotoxic activity it may also lead to NK cell dysregulation in some circumstances. In patients with metastatic melanoma NK cells were shown to be dysfunctional as a result of elevated levels of Tim-3 expression which correlated with clinical stage [35]. Taken together, improved survival may be a result of an adaptive NK cell response in the setting of a low inflammatory state, however patients with high levels of inflammation, despite being CMV+, may have worse survival outcomes due to inhibition or exhaustion of an adaptive NK cell response.

The immunosuppressive state in the tumor microenvironment may also be influenced by CMV reactivation thereby, providing tumor cells with the ability to avoid recognition and killing by the immune system [36]. Another possibility is that reactivation of CMV in tumor tissues as a result of inflammation would lead to an increased production of inflammatory factors that contribute to tumorigenesis and tumor progression [36]. Higher CMV activity has been shown to correlate with lower survival rates in patients with ovarian cancer [36]. However, a lower inflammatory response by CMV-specific T cells may regulate the capacity of tumor cells to present tumor–associated targets to cancer-directed T cells [37]. An increase in tumor antigen presentation as a result of CMV reaction and low inflammation may generate a greater immune response leading to better overall survival than patients with both CMV infection and high levels of inflammation.

A potential limitation of our study is the differences in treatment provided following cytoreductive surgery. Underlying medical comorbidities, which can influence serum CRP levels, were not taken into consideration. Another possible limitation to our study is only measuring IgG CMV levels from the blood of patients at the time of cytoreductive surgery. The results provide a measure for reactivation of the virus, but not new infection. CRP levels were also only evaluated at the time of surgery, which does not give us a full understanding of the role CRP and CMV play in altering the immune system over time.

In conclusion, CMV serostatus at the time of surgery appears to influence outcomes of epithelial ovarian cancer, particularly when serostatus is combined with CRP evaluation. The survival benefit observed in patients that had a positive CMV serostatus in the setting of low inflammation warrants further evaluation of the influence that CMV and inflammation have on the long term immune response.

Author contribution

LU, MF, and MG were involved with study conceptualization. LU, CD, AM, HN, KB, and AS, were involved with data curation. LU, MF, MG, HN, and RV performed formal analysis and investigation. RV, MG, LU, and EW acquired funding. EW, LU, MF, and MG wrote original draft. All authors reviewed and edited the final manuscript.

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA Cancer J. Clin. 70 (1) (2020) 7–30.

[2] L.A. Torre, et al., Ovarian cancer statistics, 2018, CA Cancer J. Clin. 68 (4) (2018) 284–296, https://doi.org/10.3322/caac.21456.

[3] R.J. Kurman, M. Shih Ie, The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded, Am. J. Pathol. 186 (4) (2016) 733–747.

[4] T. Baert, I. Vergote, A. Coosemans, Ovarian cancer and the immune system, Gynecol. Oncol. Rep. 19 (2017) 57–58.

[5] T. Crough, R. Khanna, Immunobiology of human cytomegalovirus: from bench to bedside, Clin. Microbiol. Rev. 22 (1) (2009) 76–98 Table of Contents.

[6] S.A. Staras, et al., Seroprevalence of cytomegalovirus infection in the United States, 1988-1994, Clin. Infect. Dis. 43 (9) (2006) 1143–1151.

[7] N. Stern-Ginossar, et al., Decoding human cytomegalovirus, Science 338 (6110) (2012) 1088–1093.

[8] L. Soroceanu, C.S. Cobbs, Is HCMV a tumor promoter? Virus Res. 157 (2) (2011) 193–203.

[9] M. Melnick, et al., Human cytomegalovirus and mucoepidermoid carcinoma of salivary glands: cell-specific localization of active viral and oncogenic signaling proteins is confirmatory of a causal relationship, Exp. Mol. Pathol. 92 (1) (2012) 118–125.

[10] R.L. Price, et al., Cytomegalovirus infection leads to pleomorphic rhabdomyosarcomas in Trp53+/− mice, Cancer Res. 72 (22) (2012) 5669–5674.

[11] C. Taher, et al., High prevalence of human cytomegalovirus proteins and nucleic acids in primary breast cancer and metastatic sentinel lymph nodes, PLoS One 8 (2) (2013), e56795, .

[12] C. Taher, et al., High prevalence of human cytomegalovirus in brain metastases of patients with primary breast and colorectal cancers, Transl. Oncol. 7 (6) (2014) 732–740.

[13] E. Paradowska, et al., Detection and genotyping of CMV and HPV in tumors and fallopian tubes from epithelial ovarian cancer patients, Sci. Rep. 9 (1) (2019) 19935.

[14] S. Shanmughapriya, et al., Viral and bacterial aetiologies of epithelial ovarian cancer, Eur. J. Clin. Microbiol. Infect. Dis. 31 (9) (2012) 2311–2317.

[15] J.W. Carlson, et al., Human cytomegalovirus in high grade serous ovarian cancer possible implications for patients survival, Medicine (Baltimore) 97 (4) (2018) e9685.

[16] L.A. Hefler, et al., Serum C-reactive protein as independent prognostic variable in patients with ovarian cancer, Clin. Cancer Res. 14 (3) (2008) 710–714.

[17] L.C. Peres, et al., High levels of C-reactive protein are associated with an increased risk of ovarian cancer: results from the ovarian cancer cohort consortium, Cancer Res. 79 (20) (2019) 5442–5451.

[18] C. Gabay, et al., Interleukin 1 receptor antagonist (IL-1Ra) is an acute-phase protein, J. Clin. Invest. 99 (12) (1997) 2930–2940.

[19] P. Loyer, et al., Interleukin 4 inhibits the production of some acute-phase proteins by human hepatocytes in primary culture, FEBS Lett. 336 (2) (1993) 215–220.

[20] A. Mackiewicz, et al., Complex of soluble human IL-6-receptor/IL-6 up-regulates expression of acute-phase proteins, J. Immunol. 149 (6) (1992) 2021–2027.

[21] J. Kodama, et al., Serum C-reactive protein as a prognostic factor in patients with epithelial ovarian cancer, Eur. J. Obstet. Gynecol. Reprod. Biol. 82 (1) (1999) 107–110.

[22] I. Kushner, M.J. Antonelli, What should we regard as an "elevated" C-reactive protein level? Ann Intern Med. 2015, p. 326 , United States.

[23] A. Macciò, C. Madeddu, Inflammation and ovarian cancer, Cytokine 58 (2) (2012) 133–147.

[24] H. Schlums, et al., Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells with altered signaling and effector function, Immunity 42 (3) (2015) 443–456.

[25] F. Cichocki, et al., CD56dimCD57+NKG2C+ NK cell expansion is associated with reduced leukemia relapse after reduced intensity HCT, Leukemia 30 (2) (2016) 456–463.

[26] A.B. Bigley, et al., Latent cytomegalovirus infection enhances anti-tumour cytotoxicity through accumulation of NKG2C+ NK cells in healthy humans, Clin. Exp. Immunol. 185 (2) (2016) 239–251.

[27] J.D. Andersen, et al., Leucine-rich alpha-2-glycoprotein-1 is upregulated in sera and tumors of ovarian cancer patients, J. Ovarian Res. 3 (2010) 21.

[28] Y. Liu, et al., The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer, BMC Cancer 17 (1) (2017) 285.

[29] M.A. McSorley, et al., C-reactive protein concentrations and subsequent ovarian cancer risk, Obstet. Gynecol. 109 (4) (2007) 933–941.

[30] B.J. Coventry, et al., CRP identifies homeostatic immune oscillations in cancer patients: a potential treatment targeting tool? J. Transl. Med. 7 (2009) 102.

[31] M.T. Madondo, et al., Variability in CRP, regulatory T cells and effector T cells over time in gynaecological cancer patients: a study of potential oscillatory behaviour and correlations, J. Transl. Med. 12 (2014) 179.

[32] M. López-Botet, A. Angulo, M. Gumá, Natural killer cell receptors for major histocompatibility complex class I and related molecules in cytomegalovirus infection, Tissue Antigens 63 (3) (2004) 195–203.

[33] B. Foley, et al., Human cytomegalovirus (CMV)-induced memory-like NKG2C(+) NK cells are transplantable and expand in vivo in response to recipient CMV antigen, J. Immunol. 189 (10) (2012) 5082–5088.

[34] A. Merino, et al., Chronic stimulation drives human NK cell dysfunction and epigenetic reprograming, J. Clin. Invest. 129 (9) (2019) 3770–3785.

[35] H. Kared, et al., Adaptive NKG2C, Front. Immunol. 9 (2018) 686.

[36] A.F. Rådestad, et al., Impact of human cytomegalovirus infection and its immune response on survival of patients with ovarian cancer, Transl. Oncol. 11 (6) (2018) 1292–1300.

[37] J.R. Lérias, et al., Clinically relevant immune responses against cytomegalovirus: implications for precision medicine, Int. J. Mol. Sci. 20 (8) (2019).