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Inflammatory and Nutritional Serum Markers as Predictors of Peri-operative Morbidity and Survival in Ovarian Cancer

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Abstract. *Aim: To identify preoperative nutritional and inflammatory markers that predict perioperative outcomes in patients with ovarian cancer (OC). Patients and Methods: Fifty patients who underwent primary debulking for advanced (stage III/IV) OC were selected from a cohort of patients who underwent surgery between 2002 and 2009. We analyzed C-reactive protein (CRP), interleukin-6 (IL6) and albumin and their impact on mortality and surgical outcomes. Results: Two patients were excluded since they did not have adequate measurements of CRP and IL6. Among the remaining patients, 25 (52%) were ≥70 years old. Nine (19%), 12 (25%) and 12 (25%) patients had low serum albumin (<3.0 g/dl), elevated CRP (≥70 mg/l) and elevated IL6 (≥24 pg/ml), respectively. Age was a significant predictor of non-home discharge (p=0.01). Low serum albumin (<3.0 g/dl) was a predictor of death within 6 month (p=0.03). Elevated CRP (≥70 mg/l) was a predictor of non-home discharge (p=0.02), death within 6 months (p=0.02), death within 12 months (p=0.04), and longer hospital stay (p=0.01). Elevated IL6 (≥24 pg/ml) was a predictor of non-home discharge (p=0.002) and surgical complications (p=0.02), and also associated with longer hospital stay (p=0.03). Conclusion: Poor nutrition and high inflammatory status negatively influence surgical and oncological outcomes of patients with OC. These preoperative markers can be used for selection of patients for neoadjuvant chemotherapy at high risk of short survival, non-home discharge and long hospital stay.*

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Epithelial ovarian cancer (OC) accounts for approximately one quarter of all gynecological malignancies, but is responsible for about half of all deaths from cancer of the female reproductive tract. Most patients present at an advanced stage of disease at the time of diagnosis and a subset will have a frail and malnourished state; identification of those patients represents an important clinical need.

Primary debulking surgery (PDS) followed by chemotherapy is the main treatment for ovarian cancer; however, alternatives such as chemotherapy alone or neoadjuvant chemotherapy followed by interval debulking surgery are also options for treatment. When patients with OC present with compromised medical or nutritional status before surgery, perioperative outcomes and survival may be negatively affected (1). In particular, low serum albumin is used at our Center to triage patients at high risk for surgical complications and perioperative mortality to neoadjuvant chemotherapy (2). Identification of patients with advanced OC at high risk for perioperative morbidity is essential for treatment planning and patient counseling.

Perioperative morbidity is an important determinant of increased hospital stay, non-home discharge, delay or inability to receive chemotherapy treatment, overall survival, and high costs (3, 4). Although some clinical variables [*e.g.* older age, stage IV of disease, higher American Society of Anesthesiologist (ASA) score, lower serum albumin] can help predict poor surgical and oncological outcomes, these models do not fully explain these adverse outcomes, and better tools for identification of these patients and understanding of their morbidity are needed.

Investigators across different oncological specialties have reported that inflammatory and nutritional markers such as C-reactive protein (CRP), interleukin-6 (IL6), albumin and Glasgow Prognostic Score (GPS, a score based on CRP and albumin levels) are correlated with performance status and survival in patients with cancer, including women with ovarian malignancy (5-8). In this pilot study, we sought to

determine the relationship between the serum inflammatory/nutritional markers (*i.e.* CRP, IL6, albumin and GPS) and perioperative and oncological outcomes in a group of patients with advanced OC undergoing PDS at a single tertiary care center. These data will be used to launch further investigation into biomarkers that influence both short-term morbidity and oncological mortality.

Patients and Methods

The pilot study utilized a random selection of 50 patients from a cohort of 313 patients who satisfied the following inclusion criteria: (i) underwent cytoreductive surgery as primary treatment for ovarian cancer at the Mayo Clinic Division of Gynecological Surgery (Rochester, MN, USA) during April 2002-June 2009 with advanced (stage IIIC/IV) OC; (ii) had consented to donate a blood sample for research purposes; (iii) had a stored frozen serum sample available for the study; and (iv) had a measurement of pre-operative albumin level within 30 days before surgery.

CRP was measured on a Roche Cobas c311 chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA) by a latex particle enhanced immunoturbidimetric assay from Roche Diagnostics. The 75th percentile was used in our analysis as a cutoff for CRP (70 mg/l). IL6 was measured by a quantitative two-site enzyme immunoassay from R & D Systems (Minneapolis, MN, USA). Lambeck et al. reported that the median serum concentration of IL6 in patients with advanced OC patients was 23.8 pg/ml, therefore a serum level ≥24 pg/ml was considered as being elevated in our analysis (10). Albumin was considered to be low if it was ≤3 mg/dl. The GPS is a score based on levels of CRP and albumin; when a patient has both CRP >10 mg/l and albumin <3.5 g/l, the score is 2, when only laboratory abnormality is present, the score is 1, and when both levels are normal, the score is 0 (5, 6). A score of 1 or more is considered abnormal.

All patients included underwent PDS *via* laparotomy. All pathology specimens were reviewed within our Institution by a gynecologic pathologist. Post-surgical complications within 30 days after surgery were classified according to the Accordion Severity Classification of Postoperative Complications (11). Length of hospital stay (LOS) was counted from the first postoperative day to discharge from the hospital. Re-admissions were not considered part of LOS. Non-home discharge was considered for all those patients who did not go to their homes to live directly after discharge from the hospital. We included in this definition both patients who died in the hospital and those who went to a skilled nursing facility after leaving our Institution.

Data were summarized using standard descriptive statistics. Duration of follow-up was calculated from the date of surgery to the date of death or last follow-up. Overall survival following surgery was estimated using the Kaplan–Meier method. Death within 6 months and death within 12 months were each evaluated as standard binary outcome measures since all of the patients who did not die had more than 12 months of follow-up. The Chi-square test was used to evaluate univariately the association between each categorical factor and each binary outcome in spite of all cells in the contingency tables not having an expected cell count >5; all cells did have an expected cell count >1. The distribution of LOS was compared between the levels of each categorical variable using the Wilcoxon rank-sum test. Multivariate analyses were not performed given the small number of events for each outcome. All calculated *p*-values were two-sided and *p*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS version 9.2 software package (SAS Institute, INC., Cary, NC, USA).

Table I. *Demographic and clinical characteristics of the 48 patients with stage IIIC/IV ovarian cancer.*

Characteristic	Total (N=48)
Age	
Mean (SD), years	68.8 (11.7)
≥70 years, n (%)	25 (52%)
Body mass index*	
Mean (SD), kg/m^2	28.4 (6.5)
≥30 kg/m^2, n (%)*	15 (34%)
Ovarian stage IV, n (%)	10 (21%)
Ovarian cancer histology, n (%)	
Serous	35 (73%)
Endometrioid	5 (10%)
Mixed	6 (13%)
Undifferentiated	2 (4%)
Albumin level	
Mean (SD), g/dl	3.7 (0.7)
≤3 g/dl, n (%)	9 (19%)
Any residual disease (>0 cm), n (%)	32 (67%)
CRP	
Mean (SD), mg/dl	54.8 (61.0)
Median (IQR), mg/dl	39.4 (10.3-69.3)
≥70 mg/dl, n (%)	12 (25%)
IL6	
Mean (SD), pg/ml	17.8 (21.7)
Median (IQR), pg/ml	13.5 (4.7-23.0)
≥24 pg/ml, n (%)	12 (25%)
GPS, n (%)	
Both normal (CRP ≤10 mg/dl, albumin ≥3.5 g/dl)	10 (21%)
One abnormal (CRP ≤10 mg/dl or albumin <3.5 g/dl)	23 (48%)
oth abnormal (CRP >10 mg/dl, albumin <3.5 g/dl)	15 (31%)

SD, Standard deviation; IQR, interquartile range; CRP, C-reactive protein; IL6, interleukin 6; GPS, glasgow prognostic score. *N=44.

Results

Among the random sample of 50 patients, two did not have adequate quality measurements of CRP and IL6 from sera, leaving 48 patients for the analysis. Compared to the remaining 263 patients not selected, the two groups were similar in terms of stage and cytoreduction, however, the study patients in the analysis were slightly older (mean age, 68.8 *vs.* 64.1 years; p=0.006), less likely to have serous histology (73% *vs.* 88%; p=0.009), and more likely to die within 1 year (27% *vs.* 15%; p=0.04) (data not shown). Table I summarizes the distribution of clinical and pathological characteristics in the study group of 48 patients. Regarding nutritional and inflammatory markers, nine patients (19%) had pretreatment albumin ≤3.0 g/ml, 12 (25%) had CRP

Table II. *Univariate analysis of predictors of early mortality and perioperative outcomes for 48 patients with advanced ovarian cancer.*

Characteristic	Non-home discharge (n=12)		Death within 6 months (n=9)		Death within 12 months (n=13)		Grade ≥3 surgical complications (n=12)	
	N (%)	*p*-Value	N (%)	*p*-Value	N (%)	*p*-Value	N (%)	*p*-Value
Age (years)		0.01		0.33		0.15		0.24
<70 (N=23)	2 (8.7)		3 (13.0)		4 (17.4)		4 (17.4)	
≥70 (N=25)	10 (40.0)		6 (24.0)		9 (36.0)		8 (32.0)	
Stage		0.68		0.31		0.30		0.04
IIIC (N=38)	9 (23.7)		6 (15.8)		9 (23.7)		7 (18.4)	
IV (N=10)	3 (30.0)		3 (30.0)		4 (40.0)		5 (50.0)	
Albumin (g/dl)		0.14		0.03		0.19		0.14
>3 (N=39)	8 (20.5)		5 (12.8)		9 (23.1)		8 (20.5)	
≤3 (N=9)	4 (44.4)		4 (44.4)		4 (44.4)		4 (44.4)	
CRP (mg/dl)		0.02		0.02		0.04		0.12
<70 (N=36)	6 (16.7)		4 (11.1)		7 (19.4)		7 (19.4)	
≥70 (N=12)	6 (50.0)		5 (41.7)		6 (50.0)		5 (41.7)	
IL6 (pg/ml)		0.002		0.14		0.57		0.02
<24 (N=36)	5 (13.9)		5 (13.9)		9 (25.0)		6 (16.7)	
≥24 (N=12)	7 (58.3)		4 (33.3)		4 (33.3)		6 (50.0)	
GPS score		0.66		0.21		0.40		0.21
Both normal (N=10)	2 (20.0)		1 (10.0)		2 (20.0)		1 (10.0)	
One abnormal (N=23)	5 (21.7)		3 (13.0)		5 (21.7)		5 (21.7)	
Both abnormal (N=15)	5 (33.3)		5 (33.3)		6 (40.0)		6 (40.0)	

CRP, C-Reactive protein; IL6, interleukin 6; GPS, glasgow prognostic score. *p*-Values were based on the chi-square test.

level ≥70 mg/l, and 12 (25%) had IL6 ≥24 pg/ml. Seven patients had both a CRP level ≥70 mg/l and IL6 ≥24 pg/ml. After calculating the GPS, 38 patients (79%) had an abnormal score (≥1).

Non-home discharge. A total of 12 (25%) patients had a non-home discharge [2 (4%) patients died in the hospital and 10 (21%) went to a skilled nursing facility]. Of the remaining 36 (75%) patients, three (6%) received home care and 33 (69%) were discharged home without nursing assistance. Age ≥70 years, CRP ≥70 mg/l and IL6 ≥24 pg/ml were significantly associated with non-home discharge based on univariate analysis (Table II).

Survival. The median overall survival for the group was 38.4 months. A total of nine (19%) patients died within 6 months. CRP ≥70 mg/l and albumin ≤3 g/dl were identified as being associated with death within the first 6 months on univariate analysis. A total of 13 (27%) patients died within the first 12 months. CRP ≥70 mg/l was also significantly associated with death within the first 12 months (Table II).

Surgical complications. A total of 12 patients had grade 3 or higher surgical complications. Stage IV disease and IL6 ≥24 pg/ml were significantly ($p<0.05$) associated with having surgical complications on univariate analysis (Table II). Complications experienced include two deaths within

Table III. *Univariate analysis of predictors of length of hospital stay. Results are based on 46 out of the 48 patients; the two patients that died in hospital were excluded from this particular analysis.*

Characteristic	Length of stay	
	Median, days	*p*-Value
Age (years)		0.09
<70 (N=22)	6.5	
≥70 (N=24)	8	
Stage		0.09
IIIC (N=37)	7	
IV (N=9)	12	
Albumin (g/dl)		0.30
>3 (N=38)	7	
≤3 (N=8)	10	
CRP (mg/dl)		0.01
<70 (N=35)	7	
≥70 (N=11)	12	
IL6 (pg/ml)		0.03
<24 (N=36)	7	
≥24 (N=10)	10	
GPS score		0.32
Both normal (N=10)	6.5	
One abnormal (N=22)	7.0	
Both abnormal (N=14)	8.0	

CRP, C-Reactive protein; IL6, interleukin 6; GPS, glasgow prognostic score. *p*-Values were based on the Wilcoxon rank-sum test or the Kruskal–Wallis test.

Table IV. *Summary table of predictors of short-term survival and perioperative outcomes in ovarian cancer based on univariate analysis.*

	Non-home discharge	Increased length of hospital stay	6-Month survival	12-Month survival	Grade ≥3 surgical complications
Univariate analysis	Age ≥70 years CRP ≥70 mg/dl IL6 ≥24 pg/ml	CRP ≥70 mg/dl IL6 ≥24 pg/ml	CRP ≥70 mg/dl Albumin ≤3 g/dl	CRP≥70 mg/dl	IL6 ≥24 pg/ml Stage IV

CRP, C-Reactive protein; IL6, interleukin 6.

30 days, three patients with post-operative myocardial infarction requiring cardiac angiography with/without intubation, five patients with a return to the operative room or invasive procedure requiring anesthesia, and one patient with renal failure.

Hospital stay. LOS ranged from 3 to 30 days, with a median of 7 days. Two patients (4%) died in hospital at 4 and 6 days, respectively, and were excluded from the analysis of this outcome. A summary of the evaluation of predictors of LOS is presented in Table III. At univariate analysis, CRP ≥70 mg/l and IL6 ≥24 pg/ml were significantly ($p<0.05$) associated with longer hospital stay. Table IV summarizes the findings of all the biomarkers and outcomes.

Discussion

The present study evaluated the role of nutritional and inflammatory markers in the prediction of post-surgical outcomes in a sample of patients with OC undergoing cytoreductive surgery for advanced-stage disease. The findings of our study demonstrate that low albumin and high levels of inflammatory markers CRP and IL6 are associated with worse perioperative outcomes (non-home discharge, long hospital stay, and surgical complications) and lower likelihood of survival at 6 and 12 months.

Frailty is a clinical state characterized by an accumulation of deficits that reflect that the individual is more vulnerable to physical stressors. Identification of frailty is important as it plays a role in an individual's ability to tolerate disease-focused treatment and in overall survival (12). However, frailty is not always self-evident, therefore serum biomarkers that may alert practitioners to a potentially frail clinical status may be useful in patients with advanced OC. Systemic inflammation (characterized by elevated markers such as CRP and IL6) and malnutrition are characteristic of frailty (13). IL6 is a proinflammatory cytokine released from immune cells, vascular endothelial cells and adipocytes that has been associated with functional decline and loss of muscle in older adults. In matched cohort studies, it is more commonly elevated in the frail cohort compared to normal matched controls (13-17). CRP is an acute-phase reactant induced by IL6, also marking systemic inflammation (12, 16).

Using these biomarkers, we may be able to better stratify patients into risk categories and subsequently adjust treatment decision-making. In approaching the patients with advanced OC, clinicians have two important decisions. The first is what surgical outcome is possible with regards to residual disease and what will be needed to achieve this result. The second decision is whether the patient can tolerate the degree of surgery needed to achieve the desired surgical result. We previously showed that albumin and age play a role in predicting surgical outcomes including morbidity and mortality (2, 18). However, in this study, we showed that elevated inflammatory markers, CRP and IL6, are associated with non-home discharge, increased LOS, severe surgical complications, and death within 6 and 12 months. This confirms findings from other institutions with similar results (8, 9, 19, 20). Somewhat surprisingly, the combined albumin/CRP score, GPS, was not associated with any outcome as has been demonstrated in other studies, however, the study was not powered to detect such a difference (5).

This study was performed in a tertiary referral center which frequently performs high complexity surgery for ovarian cancer and confined to a group of patients with advanced (stage IIIC/IV) disease who underwent primary debulking surgery. We acknowledge several limitations of our study. The retrospective nature of our investigation represents the main weakness. Secondly, among the entire cohort of women undergoing surgery for advanced OC, we selected a sample of 48 patients. Although we had performed a random selection, a skewed, medically impaired population is represented by this cohort, as demonstrated by the high number of patients with an albumin level of <3.0 g/dl. Furthermore, given the sample size and low prevalence of the outcome measures, the study had limited statistical power to identify combinations of factors in the majority of multivariate analyses. However, the present pilot study shows an important correlation between inflammatory/nutritional markers and postoperative outcomes in patients with advanced stage OC, which is hypothesis-generating.

Our study adds to the growing literature investigating biomarkers of frailty in patients with OC. While multiple prediction models exist for surgical outcomes in patients with advanced OC, easily accessible serum biomarkers are an attractive option for risk stratification of patients. This study demonstrates that CRP and IL6 may be viable serum biomarkers to aid in the identification of frail patients with OC. With further validation, this information can be incorporated into clinical practice for patient counseling and in treatment decision-making. More importantly, it can lead to further investigation into the nature of these biomarkers and others regarding disease biology and host response in OC.

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