

Serum C-Reactive Protein as Independent Prognostic Variable in Patients with Ovarian Cancer

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Abstract **Purpose:** To evaluate serum C-reactive protein (CRP) as prognostic variable in patients with epithelial ovarian cancer (EOC). **Experimental Design:** In a multicenter study, preoperative serum CRP was evaluated in 623 patients with EOC. Results were correlated with clinical data. **Results:** Mean (SD) preoperative serum CRP was 3.6 (4.8) mg/dL. Serum CRP was significantly associated with International Federation of Gynecologists and Obstetricians stage ($P < 0.001$) and postoperative residual tumor mass ($P < 0.001$) but not with histologic grade ($P = 0.1$) and type ($P = 0.7$), patients' age (Pearson's correlation coefficient = 0.05; $P = 0.2$), and serum CA 125 (Pearson's correlation coefficient = 0.02; $P = 0.6$). Patients with platinum-resistant EOC had significantly higher CRP serum levels compared with patients with platinum-sensitive EOC [6.0 (6.6) mg/dL versus 2.8 (3.8) mg/dL; $P < 0.001$]. Higher International Federation of Gynecologists and Obstetricians stage ($P < 0.001$), presence of postoperative residual tumor mass ($P < 0.001$), tumor grade ($P = 0.001$), serum CA 125 ($P = 0.03$), and serum CRP ($P = 0.001$) were independently associated with overall survival. Patients with serum CRP ≤ 1 mg/dL versus > 1 mg/dL had an overall 5-year survival of 82% versus 58.5% ($P < 0.001$). **Conclusion:** Serum CRP can be seen as a novel, widely available independent prognostic variable of ovarian cancer.

C-reactive protein (CRP) is one of the most important acute-phase proteins produced predominantly by hepatocytes rising rapidly in response to inflammation (1, 2). CRP has both proinflammatory and anti-inflammatory actions, and it is uncertain which is predominant. Proinflammatory effects include the induction of monocytes. Anti-inflammatory actions are reflected by the diminished accumulation of neutrophils at inflammatory sites due to reduced neutrophil adhesion to the endothelium and the noninflammatory clearance of apoptotic

cells (1, 2). Circulating serum CRP is routinely measured in clinical laboratories as marker for various acute and chronic inflammatory diseases (3–5).

The pathogenesis and development of ovarian cancer have also been closely linked to inflammatory processes (6, 7). The inflammatory response promotes carcinogenesis by damaging DNA, stimulating angiogenesis and cell proliferation, and inhibiting apoptosis (8, 9). Various proinflammatory cytokines, such as interleukin-1, interleukin-6, tumor necrosis factor- α , IFN- γ , and tumor growth factor, all known to stimulate CRP production, influence survival, growth, mutation, proliferation, differentiation, and migration of tumor cells (6, 7, 10, 11).

Serum CRP has been shown to parallel carcinogenesis possibly as an expression of the host defense reaction or as paraneoplastic syndrome (1, 3). Therefore, serum CRP has been investigated as risk factor and prognostic variable in various human malignancies, such as colon (12), esophageal (13), hepatocellular (14), and renal cell (15) cancer. Few data are available on the role of serum CRP in gynecologic malignancies. Preliminary data suggest a possible prognostic value in patients with ovarian cancer (16).

Tumor stage and postoperative residual tumor mass at primary cytoreductive surgery have been shown to most reliably predict outcome in patients with ovarian cancer (17). Clinical decision making with respect to adjuvant therapy is largely based on International Federation of Gynecologists and Obstetricians (FIGO) stage and tumor grade, especially in early-stage disease. The standard concept of six cycles of a platinum/taxane combination as adjuvant chemotherapy for ovarian

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cancer has recently been challenged (18, 19). Omission of chemotherapy for adequately staged early-stage disease (20), a neoadjuvant chemotherapy approach for patients expected not to be optimally debulked at primary cytoreductive surgery (21), and consolidation chemotherapy for patients at high risk for recurrent disease have been advocated (22). Additional prognostic variables to more individually tailor adjuvant therapy would be of considerable clinical value.

Therefore, the aim of the present study was to investigate the clinical value of serum CRP as independent prognostic variable in a large multicenter study of patients with ovarian cancer.

Materials and Methods

Patients. A total of 623 patients with epithelial ovarian cancer were included in the present retrospective multicenter study (Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria: $n = 208$; Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria: $n = 192$; Department of Obstetrics and Gynecology, Charité/Campus Virchow-Klinikum, University Medicine of Berlin, Berlin, Germany: $n = 99$; Landeskrankenhaus Klagenfurt, Klagenfurt, Austria: $n = 64$; Wilhelminenspital, Vienna, Austria: $n = 29$; Sozialmedizinisches Zentrum Süd, KFJ, Vienna, Austria: $n = 31$). The respective Institutional Review Boards approved the present study. Data were collected with chart review. Before elective surgery, an acute infection was ruled out by a physical examination, measuring body temperature, and respective blood tests.

Patients were treated according to standards of the respective institution with hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or paraaortic lymphadenectomy, appendectomy, and omentectomy. All patients with tumor stages Ic to III and all patients with clear cell carcinoma received a platinum-based chemotherapy. All patients were followed up in 3-month intervals, including vagino-rectal palpation, abdominal ultrasound examination, and serum tumor marker evaluation. In cases of clinically doubtful findings and/or tumor marker elevation, computed tomography was done. The mean duration of follow-up was 25.5 (24.1) months. Patient charts were reviewed to obtain clinical data about age, FIGO tumor stage, tumor grade, amount of postoperative residual tumor mass after primary surgery, histologic type, preoperative serum CA 125, and time of death or time of last follow-up. Mean patient's age at diagnosis, distribution of tumor stage, amount of postoperative residual tumor mass, and tumor grade were not different between study centers. Patients with platinum-resistant and platinum-sensitive tumors were defined as having a time with no evidence of disease ≤ 6 months versus > 6 months after completion of primary chemotherapy.

CRP measurement. Patients' blood was obtained before surgery by peripheral venous puncture. CRP serum levels were measured as part of the clinical routine by a modified latex-enhanced immunoturbidimetric assay using a CRP Latex kit (Olympus Life and Material Science Europe) according to the manufacturer's instructions (23). Serum levels ≤ 1 mg/dL were defined as normal. The manufacturer claims an intra-assay variability between 1.64% and 3.34%. Serum CRP levels were not assessed expressly as part of the study but were ascertained as part of clinical routine. Of note, serum CRP levels were not assayed at one central laboratory to better reflect clinical practice, but all clinical laboratories used the same assay kit.

Table 1. Patients' characteristics and CRP serum levels in patients with ovarian cancer broken down by clinicopathologic variables

Variable	n or mean (SD)	Mean (SD) CRP serum levels (mg/dL)	P
Patients with epithelial ovarian cancer	623	—	—
Age at first diagnosis (y)	60.5 (13.7)	—	—
Tumor stage			
FIGO I	143	1.9 (3.0)	<0.0001*
FIGO II	44	2.1 (2.6)	
FIGO III	346	4.3 (5.3)	
FIGO IV	90	4.7 (5.6)	
Postoperative residual tumor mass after surgery (cm)			
≤ 2	459	2.9 (4.5)	<0.0001 [†]
> 2	164	5.7 (5.3)	
Tumor grade			
G ₁	89	2.7 (5.2)	0.1*
G ₂	218	3.4 (4.7)	
G ₃	316	3.9 (4.7)	
Histologic type			
Serous	401	3.6 (4.7)	0.7 [†]
Mucinous	68		
Endometrioid	89		
Others	65		
Mucinous, endometrioid, and all others combined	222	3.5 (5.0)	
Length of follow-up (mo)	25.5 (24.1)	—	—
Status at last observation			
Alive with no evidence of disease	342	—	—
Alive with stable disease	66	—	—
Progressive disease	64	—	—
Dead as a result of disease	131	—	—
Dead as a result of other causes	15	—	—
Lost to follow-up	5	—	—

*One-way ANOVA.

[†] t test.

Table 2. Univariate and multivariate survival analysis in patients with ovarian cancer

	Univariate <i>P</i>	Multivariate <i>P</i> *	Multivariate HR (95% CI)
Tumor stage † (FIGO I vs II vs III vs IV)	<0.0001 ‡	<0.0001	1.9 (1.5-2.5)
Postoperative residual tumor mass † (≤2 cm vs >2 cm)	<0.0001 ‡	<0.0001	2.3 (1.6-3.3)
Histologic grade † (G ₁ vs G ₂ vs G ₃)	<0.0001 ‡	0.001	1.6 (1.2-2.2)
Age †	<0.0001 §	0.2	1 (0.9-1.1)
Histologic type † (serous vs all others)	0.003 ‡	0.3	1.2 (0.8-1.8)
Serum CA 125 †	0.004 §	0.03	1.03 (1.02-1.2)
Serum CRP †	<0.0001 §	0.001	1.05 (1.02-1.08)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

*Multivariate Cox regression analysis.

† Variables in the multivariate analysis.

‡ Log-rank test.

§ Univariate Cox regression analysis.

Statistics. Values are given as means (SD). Variables were compared using Pearson’s correlation coefficient, *t* test, and one-way ANOVA. Survival probabilities were calculated by univariate Kaplan-Meier analysis or univariate and multivariate Cox regression models. The results were analyzed for the end point of overall survival. We included all patients into our survival analysis. Survival times of patients with no evidence of disease, with stable disease as defined by Response Evaluation Criteria in Solid Tumors criteria, and patients having died of non – cancer-related events were censored with the last follow-up date. Survival times of patients with cancer-related death and of patients with progressive disease at the time of last follow-up were not censored. *P* values of <0.05 were considered statistically significant. For statistical analysis, we used the Statistical Package for the Social Sciences statistical software (version 11.0; SPSS, Inc.).

Results

Patients’ characteristics are given in Table 1. Mean (SD) preoperative serum CRP in patients with epithelial ovarian cancer was 3.6 (4.8) mg/dL. Mean CRP serum levels between study centers [Department of Obstetrics and Gynecology, Medical University of Vienna: 3.7 (5.3) mg/dL; Department of Obstetrics and Gynecology, Innsbruck Medical University: 3.6 (4.5) mg/dL; Department of Obstetrics and Gynecology, Charité/Campus Virchow-Klinikum, University Medicine of Berlin: 3.7 (4.9) mg/dL; Landeskrankenhaus Klagenfurt: 2.6 (2.9) mg/dL; Wilhelminenspital: 5.0 (5.4) mg/dL; Sozialmedizinisches Zentrum Süd, KFJ: 3.3 (5.7) mg/dL] were similar (*P* = 0.3).

Serum CRP was significantly correlated with FIGO stage and postoperative residual tumor mass but not with histologic grade and type, patients’ age (Pearson’s correlation coefficient = 0.05; *P* = 0.2), and serum CA 125 (Pearson’s correlation coefficient = 0.02; *P* = 0.6; Table 1). Patients with platinum-resistant tumors (*n* = 159) had significantly higher CRP serum levels compared with patients with platinum-sensitive tumors [*n* = 464; 6.0 (6.6) mg/dL versus 2.8 (3.8) mg/dL; *P* < 0.001]. In a univariate survival analysis, FIGO stage, postoperative residual tumor mass, histologic grade, histologic type (serous versus all others), patients’ age, serum CA 125, and serum CRP were associated with overall survival (Table 2). In the multivariate Cox regression model, higher FIGO stage, presence of postoperative residual tumor mass, higher histologic grade,

higher serum CA 125, and higher serum CRP were associated with a shortened overall survival (Table 2; Fig. 1). Patients with serum CRP ≤1 mg/dL versus >1 mg/dL had an overall 5-year survival of 82% versus 58.5% (*P* < 0.001; Fig. 1).

When univariate survival analysis was done in all study centers separately, serum CRP levels were associated with overall survival in five of six centers (Department of Obstetrics and Gynecology, Medical University of Vienna: *P* < 0.001; Department of Obstetrics and Gynecology, Innsbruck Medical University: *P* < 0.001; Department of Obstetrics and Gynecology, Charité/Campus Virchow-Klinikum, University Medicine of Berlin: *P* = 0.004; Landeskrankenhaus Klagenfurt: *P* = 0.02; Wilhelminenspital: *P* = 0.02; Sozialmedizinisches Zentrum Süd, KFJ: *P* = 0.4).

A subgroup analysis was done for patients with FIGO stage I ovarian cancer. Five and four patients experienced progressive disease and cancer-related death during follow-up, respectively. Due to the low number of events, only univariate analysis

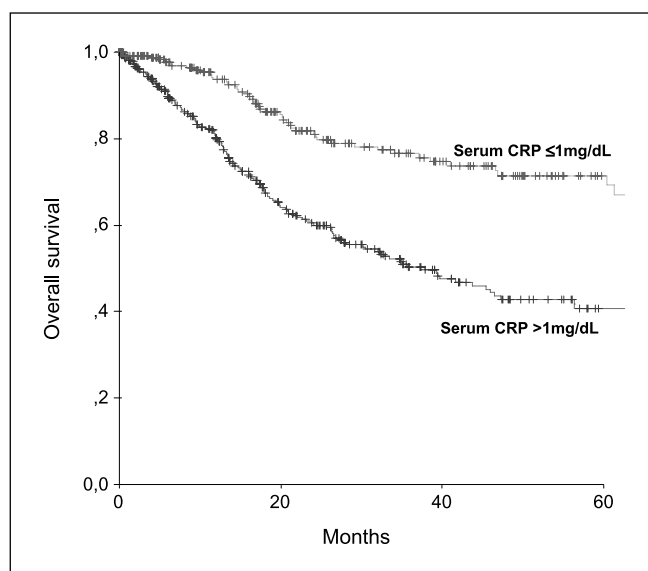


Fig. 1. Kaplan-Meier curves for overall survival of patients with ovarian cancer broken down by serum CRP.

was done. Serum CA 125 levels ($P = 0.4$) and serum CRP levels ($P = 0.4$) were not associated with survival. Nine of 45 patients with serum CA 125 levels in the reference range had abnormal CRP serum levels >1 mg/dL.

Discussion

In various human malignancies, clinical decision making is based on established histopathologic prognosticators. Recently, several new prognostic variables, such as immunohistochemically detected Her-3 (24), serum vascular endothelial growth factor (25), serum tissue factor (26), and serum p53 (27) antibodies, have been also been published to better define ovarian cancer patients' risk profiles.

Several studies dealing with cytokines and their prognostic effect have been published in ovarian cancer (25, 28, 29). A clinical value has not yet been established. Promising data on the prognostic effect of serum CRP in various malignancies as well as primary data in ovarian cancer have been published (16).

Therefore, we ascertained the prognostic value of serum CRP in patients with ovarian cancer. To our best knowledge, the present multicenter study is the largest series to date with respect to any serum marker in ovarian cancer patients. The obtained results were promising. Elevated serum CRP levels were found to be associated with higher FIGO stage, indicating that serum CRP can be seen as bulk marker of ovarian cancer. Furthermore, higher preoperative serum CRP was associated with an increased risk for suboptimal debulking (i.e., postoperative residual tumor mass >2 cm) at primary surgery. This might possibly be useful to select patients who benefit from neoadjuvant chemotherapy versus those who benefit from primary cytoreductive surgery. High serum CRP might reflect a high metastatic potential, as inflammatory cytokines in general and CRP in particular are known to promote metastatic spread by stimulating angiogenesis, increasing vascular permeability, and acting as an endothelial cell mitogen (5).

About prognosis, serum CRP was, besides all clinically established prognosticators, independently associated with overall survival. This finding is in accordance with other inflammation-related cytokines, such as vascular endothelial growth factor (25), interleukin-6 (28), and interleukin-12 (29). In contrast to these variables, serum CRP is evaluated as marker of inflammation in daily clinical routine in laboratories worldwide. A commercially available test system is readily available. Measurement of serum CRP is relatively cheap and easy to perform. Additionally, we evaluated a potential cutoff value for serum CRP. Patients with a negative (≤ 1 mg/dL) CRP serum had a significantly better prognosis than those with an elevated (>1 mg/dL) serum CRP.

The results of this study might suggest that serum CRP could serve as potentially clinically useful marker in patients with ovarian cancer. (a) Elevated preoperative serum CRP predicts the presence of residual tumor after primary cytoreductive surgery. This might possibly be useful to select patients who benefit from neoadjuvant chemotherapy versus those who benefit from primary cytoreductive surgery. High serum CRP might reflect a high metastatic potential as inflammation is known to promote metastatic spread by stimulating angiogenesis. (b) Serum CRP levels were found to be associated with the response to platinum-based chemotherapy possibly allowing to modify chemotherapy regimens. (c) Besides the already established prognosticators FIGO stage, residual tumor mass, and patients' age, serum CRP was independently associated with prognosis in all patients with ovarian cancer, possibly defining a subset of patients with bad prognosis requiring intense therapy. As potential shortcoming of our study, we have to acknowledge that data on comorbidities, such as diabetes, obesity, or smoking, which can possibly influence serum CRP levels, are not known in our series.

Based on the number of patients included and the multicenter study design, we believe that our results are promising. Serum CRP could be used as novel, widely available, and relatively cheap independent prognostic variable of ovarian cancer.

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