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ORIGINAL RESEARCH

The Role of Perioperative C-Reactive Protein in Predicting the Prognosis of Epithelial Ovarian Carcinoma

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Background: Increasing epidemiological evidence supported that chronic inflammatory factors might be involved in the carcinogenesis and progression of various cancers. The present study tried to investigate the prognostic value of perioperative C-reactive protein (CRP) in prognosis of patients with epithelial ovarian carcinoma (EOC) from a tertiary university teaching hospital.

Methods: The cutoff value of CRP was calculated according to receiver operating characteristic (ROC) curve. Variables were compared using Chi-square test. Progress-free survival (PFS) and overall survival (OS) time were assessed by Kaplan–Meier (KM) survival analysis and Log rank test based on serum CRP level. Univariate and multivariate Cox regression analyses were applied for assessing the relationship between clinicopathological parameters and survival.

Results: Higher perioperative CRP levels (preoperative ≥5.15 mg/L and postoperative ≥72.45 mg/L) were significantly associated with serous tumor, high-grade, advanced stage, elevated preoperative CA125, suboptimal surgery, chemotherapy resistance, recurrence and death in EOC ($P < 0.01$). KM analysis suggested patients with elevated preoperative, postoperative and perioperative CRP had shorter survival ($P < 0.01$). Elevated perioperative CRP was an independent risk factor for PFS (HR 1.510, 95% CI 1.124–2.028; $P = 0.006$) and OS (HR 1.580, 95% CI 1.109–2.251; $P = 0.011$). Similar results were obtained for elevated preoperative CRP. Subgroup analysis further suggested that elevated perioperative CRP was also an independent risk factor for prognosis in advanced stage and serous EOC.

Conclusion: Elevated perioperative CRP was an independent risk factor for poorer prognosis of EOC, particularly in advanced stage and serous patients.

Keywords: epithelial ovarian carcinoma, perioperative C-reactive protein, prognosis

Introduction

Epithelial ovarian carcinoma (EOC) remains the leading cause of death from gynecologic tumors.[1–3] Despite the improvements in surgical techniques and chemotherapeutic regimens, the 5-year survival rate for EOC is still poor.[4,5] Although the exact cause of EOC has not been fully elucidated, increasing epidemiological evidence supported that chronic inflammation might be one mechanism of carcinogenesis and progression in various cancers.[6–10] Thus, the evaluation of the relationships between inflammatory markers and disease progression of EOC might help guide clinical management and predict the prognosis of EOC.

C-reactive protein (CRP), released predominantly by hepatocytes upon tissue injury and inflammation, is an important and non-specific inflammatory factor.[11,12] Accumulating evidences have revealed the association between CRP and the risk of various cancers.[6,13–19] Peres et al[6] found women with CRP concentrations >10mg/L showed a 67% increased risk of ovarian cancer compared to <1mg/L (OR=1.67, 95% CI 1.12–2.48; P=0.01). And CRP concentration >10mg/L was

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also positively associated with risk of mucinous (OR=9.67, 95% CI 1.10–84.80; P=0.04) and endometrioid carcinoma (OR=3.41, 95% CI 1.07–10.92; P=0.03).

In addition to the role in carcinogenesis, promising data on the prognostic role of preoperative CRP in various malignancies including EOC have been reported.[11,20–24,] However, the literature about EOC was limited and the sample size of most studies was small,[25–29] which would prevent well-powered analyses of potential heterogeneity of the association between clinical parameters and patient prognosis. Even in Hefler's report which recruited 623 patients with EOC, they did not analyze the relationship of perioperative (combined preoperative with postoperative) CRP and survival or conduct subgroup analysis,[11] which might weaken the evidences for CRP as an independent prognostic factor of EOC. Furthermore, the cutoff value of preoperative CRP in different studies was varied.[11,24] Lu et al[24] found that the average preoperative CRP level in 107 Chinese patients with EOC was lower than previous reports for Caucasian cases, and deduced it might reflect ethnic variations. However, no study was reported about the role of both preoperative and postoperative (perioperative) CRP in the prognosis of EOC up to date. Therefore, the aim of the present retrospective cohort study was to comprehensively investigate the clinical relationship between perioperative serum CRP and prognosis of EOC in a relatively large sample size of Chinese population, which permitted us reduce disease heterogeneity by subgroup analysis. Hope to provide better understanding on how CRP influences prognosis and provide insights on the potential strategy of clinical management of EOC.

Materials and Methods

Patients and Data Collection

We retrospectively reviewed the records of ovarian cancer at Women's hospital, Zhejiang University School of Medicine between 2002.01.01 and 2016.12.31. The study was approved by the Ethical Committee of women's hospital, Zhejiang University School of Medicine (IRB-20200230-R). Owing to the retrospective character and the difficulty of recalling all enrolled patients, informed consent was specifically waived by the ethics committee. All the researcher declared to protect patient data confidentiality and compliance with the Declaration of Helsinki. The enrolled patient should meet all the following inclusion criteria: (1) initial treatment was surgery including comprehensive surgical staging or cytoreductive surgery, followed by platinum-based chemotherapy in patients with stage Ic-IV, (2) histological diagnosis of EOC confirmed by Paraffin Section, (3) preoperative blood routine showed normal white blood cell and neutrophil count, (4) available serum CRP within 3 days before operation (preoperative) or within 7 days after operation (postoperative), and (5) available follow-up data of recurrence and death. Exclusion criteria included (1) primary other cancer; (2) the increase of CRP was caused by infection, connective tissue diseases or other inflammatory conditions, judged body temperature, clinical manifestation and auxiliary examination; (3) postoperative complications developed (including postoperative infection and massive bleeding); (4) the first dose of chemotherapy was delayed more than weeks after surgery; (5) only postoperative CRP results were available. Due to the retrospective character of the present study, patients with preoperative CRP results were included for evaluating the prognostic value of preoperative CRP, while patients with both preoperative and postoperative CRP results were included for perioperative CRP.

The clinical information of each selected patient was collected from the hospital database, and survival status was followed up by phone. The variables included age at diagnosis, histological type, FIGO stage, tumor grade, preoperative and postoperative serum CRP, preoperative serum CA125, postoperative residual tumor after primary surgery, chemotherapy sensitivity and the time of recurrence, death or last follow-up. Serum CRP was detected by immunoturbidimetry as part of the clinical routine management. Chemotherapy resistance was defined as having a time with recurrence of disease ≤6 months after completion of primary chemotherapy. Overall survival (OS) time was calculated as the interval between the date of primary surgery and the date of last follow-up or death. PFS was calculated as the interval from the date of primary surgery to the time of detected recurrence or progression.

Statistical Analysis

SPSS 20.0 statistical software was used for statistical analyses. The cutoff value of preoperative and postoperative CRP was 5.15 and 72.45mg/L, respectively, which was determined by Youden Index of the ROC curve. Variables were compared by Chi-square test. Spearman correlation analysis was used to analyze the correlation between preoperative CRP and postoperative CRP. PFS and OS were assessed by Kaplan–Meier survival (KM) analysis and Log rank test based on serum CRP level. Univariate and multivariate Cox regression analyses were applied for assessing the relationship between clinicopathological parameters and survival. For all analyses, an alpha level <0.05 was considered statistically significant.

Results

The Clinical-Pathological Characteristics of EOC Patients and Their Relationship with Perioperative CRP Level

A total of 654 EOC patients who met the included and excluded criteria were included for evaluating the prognostic value of preoperative CRP. Due to the retrospective character of the present study, 172 out of 654 EOC patients did not receive postoperative CRP measurement. Thus, only 482 EOC patients were included for evaluating the prognostic value of perioperative CRP (both preoperative and postoperative CRP). The median follow-up period of 654 EOC was 49 months, ranged from 3 to 190 months. There was a positive correlation between preoperative CRP and postoperative CRP (p=0.000). However, the correlation coefficient was only 0.315, which may be affected by pathological type, grade, FIGO stage, postoperative residual lesions and other clinical parameters.

As shown in Table 1 and Supplementary Table S1, Chi-square test suggested that older age, serous carcinoma, high grade, advanced stage, higher preoperative CRP, higher preoperative CA125, higher postoperative CRP, higher perioperative CRP (both preoperative CRP ≥5.15mg/L and postoperative CRP ≥72.45mg/L), chemotherapy resistance and larger postoperative residual tumor (≥1cm) significantly correlated with poorer prognosis of EOC patients. However, subgroup analysis according to tumor stage found that histological type and tumor grade were no longer associated with the prognosis of EOC, except for the relationship between histological type and prognosis in advanced-stage subgroup from 482 EOC patients (Table 1). Most of the non-serous tumors were in early stage with good prognosis. But once they progressed into advanced stage, the mortality of non-serous EOC would be higher than that of serous tumors (Table 1).

Since CRP levels were significantly associated with the prognosis of EOC, the relationship between CRP level (preoperative, postoperative and perioperative CRP, respectively) and clinical-pathological characteristics of EOC were further analyzed. The results suggested higher preoperative, postoperative and perioperative CRP levels were all significantly associated with advanced stage, postoperative residual tumor (≥1cm), chemotherapy resistance, recurrence, and death in EOC patients (all P<0.01). Higher preoperative and perioperative CRP were also associated with high-grade tumor and increased CA125 level, while postoperative and perioperative CRP levels were both significantly associated with serous tumor (P<0.05) (Table 2).

Independent Risk Factors Related to Prognosis in EOC Patients

As shown in Table 3, univariate Cox regression analysis identified histological type, tumor grade, FIGO stage, preoperative CA125 level, postoperative residual tumor size and preoperative CRP level are significant prognostic factors related with PFS and OS (all p<0.001). In addition, age (p=0.013) was significantly associated with OS, but not associated with PFS. Further multivariate analysis showed that elevated perioperative CRP (both increased) was an independent risk factor for PFS (HR 1.510, 95% CI 1.124–2.028; p = 0.006) and OS (HR 1.580, 95% CI 1.109–2.251; p = 0.011), in addition to serous tumor, advanced stage and suboptimal surgery (residual tumor ≥1cm). Similar results were also validated in 654 patients with preoperative CRP results (Supplementary Table S2), except for serous tumor (elevated preoperative CRP, advanced stage and suboptimal surgery for PFS:HR=1.506, 95% CI 1.206–1.881; 6.192, 95% CI 4.094–9.366 and 1.561, 95% CI 1.228–1.985; for OS:HR=1.646, 95% CI 1.270–2.134; 9.729, 95% CI 5.537–17.093 and 1.929, 95% CI 1.465–2.539 seperately; all p = 0.000).

Table 1 The Clinicopathological Characteristics of EOC Patients with Perioperative CRP

Criterion		Total Patients	No Recurrence	Recurrence	*P*	Survival	Death	*P*
Number		482	249 (51.7%)	233 (48.3%)		326 (67.6%)	156 (32.4%)	
Age; Median (range)		51.5 (16–79)	51 (16–75)	52 (23–79)	0.002	50 (16–77)	53 (23–79)	0.001
Histological type					0.000			0.009
Serous		343 (71.2%)	145 (42.3%)	198 (57.7%)		217 (63.3%)	126 (36.7%)	
Clear cell		61 (12.7%)	44 (72.1%)	17 (27.9%)		47 (77.0%)	14 (23.0%)	
Mucinous		36 (7.5%)	32 (88.9%)	4 (11.1%)		32 (88.9%)	4 (11.1%)	
Endometrioid		18 (3.7%)	10 (55.6%)	8 (44.4%)		12 (66.7%)	6 (33.3%)	
Other		24 (5.0%)	18 (75.0%)	6 (25.0%)		18 (75.0%)	6 (25.0%)	
Tumor grade					0.000			0.000
Low-grade		111 (23.0%)	90 (81.1%)	21 (18.9%)		94 (84.7%)	17 (15.3%)	
High-grade		371 (77.0%)	159 (42.9%)	212 (57.1%)		232 (62.5%)	139 (37.5%)	
FIGO stage					0.000			0.000
I		148 (30.7%)	135 (91.2%)	13 (8.8%)		142 (95.9%)	6 (4.1%)	
II		40 (8.3%)	29 (72.5%)	11 (27.5%)		34 (85.0%)	6 (15.0%)	
III		279 (57.9%)	81 (29.0%)	198 (71.0%)		143 (51.3%)	136 (48.7%)	
IV		15 (3.1%)	4 (26.7%)	11 (73.3%)		7 (46.7%)	8 (53.3%)	
Preoperative CRP; Median (range)		3.65 (0–168.00)	2.60 (0–136.80)	5.50 (0–168.00)	0.003	2.70 (0–136.80)	6.66 (0–168.00)	0.002
Postoperative CRP; Median(range)		55.50 (0–334.00)	49.10 (0–282.30)	63.20 (1.80–334.00)	0.001	50.90 (0–282.30)	73.30 (4.30–334.00)	0.010
Perioperative CRP					0.000			0.000
Other		382 (79.3%)	217 (56.8%)	165 (43.2%)		276 (72.3%)	106 (27.7%)	
Both increased*		100 (20.7%)	32 (32.0%)	68 (68.0%)		50 (50.0%)	50 (50.0%)	
Preoperative CA125 Median (range)		238.65 (6.60–22,289.0)	102.90 (6.60–9744.0)	562.2 (10.20–22,289.00)	0.000	152.90 (6.60–9868.00)	571.50 (12.40–22,289.0)	0.000
Postoperative residual tumor					0.000			0.000
	<1cm	395 (82.0%)	237 (60.0%)	158 (40.0%)		302(76.5%)	93(23.5%)	
	≥1cm	87 (18.0%)	12 (13.8%)	75 (86.2%)		24 (27.6%)	63 (72.4%)	
Chemotherapy resistance					0.000			0.000
	No	403 (83.6%)	249 (61.8%)	154 (38.2%)		316 (78.4%)	87 (21.6%)	
	Yes resistance	79 (16.4%)	0 (0.0%)	79 (100.0%)		10 (12.7%)	69 (87.3%)	
Tumor grade					0.000			0.000
Early stage	Low-grade	95 (50.5%)	86 (90.5%)	9 (9.5%)	0.172	89 (93.7%)	6 (6.3%)	0.970
	High-grade	93 (49.5%)	78 (83.9%)	15 (16.1%)		87 (93.5%)	6 (6.5%)	
Advanced stage	Low-grade	16 (5.4%)	4 (25.0%)	12 (75.0%)	0.943	5 (31.2%)	11 (68.8%)	0.104
	High-grade	278 (94.6%)	81 (29.1%)	197 (70.9%)		145 (52.2%)	133 (47.8%)	

(*Continued*)

Table 1 (Continued).

Criterion		Total Patients	No Recurrence	Recurrence	*P*	Survival	Death	*P*
Histological type					0.000			0.000
Early stage	Non-serous	111 (59.0%)	97 (87.4%)	14 (12.6%)	0.940	101 (91.0%)	10 (9.0%)	0.143
	Serous	77 (41.0%)	67 (87.0%)	10 (13.0%)		75 (97.4%)	2 (2.6%)	
Advanced stage	Non-serous	28 (9.5%)	7 (25.0%)	21 (75.0%)	0.631	8 (28.6%)	20 (71.4%)	0.012
	Serous	266 (90.5%)	78 (29.3%)	188 (70.7%)		142 (53.4%)	124 (46.6%)	

Notes: *preoperative CRP ≥5.15mg/L and postoperative CRP ≥72.45mg/L.

Subgroup analysis according to tumor stage suggested that no prognostic factor was associated with PFS and OS in EOC of early stage due to the good prognosis (Table 4). While for advanced stage subgroup, univariate and multivariate Cox regression analyses validated that elevated perioperative CRP and suboptimal surgery were independent risk factors for poorer prognosis (Table 4). As we know, non-serous tumor was an independent risk factor for OS in 482 patients with perioperative results and advanced-stage subgroup (Table 3–4), which was contrary to the results from 654 patients with preoperative CRP result (Table 2). Thus, subgroup analyses according to histological type were further conducted. Our results suggested perioperative CRP has no significant relationship with the prognosis in non-serous EOC. While in serous EOC, advanced stage, suboptimal surgery and elevated perioperative CRP were independent risk factors for poorer prognosis (Table 5).

Elevated Perioperative CRP Level Was Associated with Shorter PFS and OS

As shown in Figure 1, EOC patients with elevated preoperative CRP had shorter PFS (22.0 vs 119.0 months) and OS (67.0 vs not reached) compared to preoperative CRP <5.15mg/L. EOC patients with elevated postoperative CRP also had shorter PFS (29.0 vs 119.0 months) and OS (76.0 vs not reached) compared to postoperative CRP <72.45 mg/L. Consistently, EOC patients with elevated perioperative CRP had shorter PFS (17.0 vs 119.0 months) and OS (50.0 vs not reached) compared to other patients. These results suggested that elevated perioperative CRP level (both preoperative CRP ≥5.15 mg/L and postoperative CRP ≥72.45 mg/L) is a consolidated predictive factor for poorer prognosis in EOC patients. The predicting capacity of perioperative CRP (combined with preoperative and postoperative CRP) was significantly higher than that predicted by preoperative and postoperative CRP alone.

Discussion

Although the prognosis of EOC depends on a variety of factors, clinical decision-making is still based on established histopathologic prognosticators.[11] Previous studies have recognized that inflammatory-related cytokines play important regulatory roles in tumorigenesis, cancer progression and metastasis.[18,19] The tumor microenvironment of EOC is rich in a variety of proinflammatory cytokine and chemokines, such as interleukin (IL)-1, IL-6, transforming growth factor-β and interferon-r, which can affect cellular communication, stimulate CRP production and are critical for tumor growth, invasion, and migration.[30,31] Increasing evidences supported that inflammatory factors including CRP, were not only secreted by hepatocytes as an inflammatory response to infection, trauma and malignant tumors but also derived from tumor cells themselves.[32–34] Compared with other inflammatory factors, serum CRP is a marker detected in daily clinical practice, which would be easy to perform.

The association between elevated pretreatment CRP levels and poor prognosis has been studied in different cancers including EOC.[6,11,17,20–24,35–37] Knittelfelder et al validated that pre-treatment CRP level represented an independent prognostic factor for survival in patients with oral and oropharyngeal cancer, particularly in those treated with definitive chemo-radiotherapy.[20] Hefler et al also reported that preoperative serum CRP could serve as clinically useful marker in 623 patients with EOC and found that the patients with CRP ≤1 mg/dl had better 5-year OS than those >1 mg/dl (82% vs 58.5%).[11] While Lu et al found that CRP > 8 mg/l was related with poorer 5-year

Table 2 The Relationship Between Perioperative CRP Level and Clinicopathological Characteristics of EOC Patients

Criterion		n	Preoperative CRP		*P*	n	Postoperative CRP		*P*	Perioperative CRP		*P*
			No Increased	Increased			No Increased	Increased		Other	Both Increased*	
Age	<51y	307	190(61.9%)	117(38.1%)	0.238	224	146(65.2%)	78(34.8%)	0.134	186(83.0%)	38(17.0%)	0.056
	≥51y	347	199(57.3%)	148(42.7%)		258	151(58.5%)	107(41.5%)		196(76.0%)	62(24.0%)	
Histological type	Non-serous	190	121(63.7%)	69(36.3%)	0.161	139	102(73.4%)	37(26.6%)	0.001	125(89.9%)	14(10.1%)	0.000
	Serous	464	268(57.8%)	196(42.2%)		343	195(56.9%)	148(43.1%)		257(74.9%)	86(25.1%)	
FIGO stage	I–II	241	174(72.2%)	67(27.8%)	0.000	188	132(70.2%)	56(29.8%)	0.002	172(91.5%)	16(8.5%)	0.000
	III–IV	413	215(52.1%)	198(47.9%)		294	165(56.1%)	129(43.9%)		210(71.4%)	84(28.6%)	
Tumor grade	Low-grade	146	100(68.5%)	46(31.5%)	0.012	111	75(67.6%)	36(32.4%)	0.142	99(89.2%)	12(10.8%)	0.003
	High-grade	508	289(56.9%)	219(43.1%)		371	222(59.8%)	149(40.2%)		283(76.3%)	88(23.7%)	
Preoperative CA125	<35U/mL	102	80(78.4%)	22(21.6%)	0.000	76	52(68.4%)	24(31.6%)	0.184	71(93.4%)	5(6.6%)	0.001
	≥35U/mL	552	309(56.0%)	243(44.0%)		406	245(60.3%)	161(39.7%)		311(76.6%)	95(23.4%)	
Postoperative residual tumor	<1cm	519	346(66.7%)	173(33.3%)	0.000	395	259(65.6%)	136(34.4%)	0.000	333(84.3%)	62(15.7%)	0.000
	≥1cm	135	43(31.9%)	92(68.1%)		87	38(43.7%)	49(56.3%)		49(56.3%)	38(43.7%)	
Chemotherapy resistance	No	538	348(64.7%)	190(35.3%)	0.000	403	260(64.5%)	143(35.5%)	0.003	334(82.9%)	69(17.1%)	0.000
	Yes	116	41(35.3%)	75(64.7%)		79	37(46.8%)	42(53.2%)		48(60.8%)	31(39.2%)	
Recurrence	No	311	219(70.4%)	92(29.6%)	0.000	249	172(69.1%)	77(30.9%)	0.001	217(87.1%)	32(12.9%)	0.000
	Yes	343	170(49.6%)	173(50.4%)		233	125(53.6%)	108(46.4%)		165(70.8%)	68(29.2%)	
Death	No	4055	273(67.4%)	132(32.6%)	0.000	326	221(67.8%)	105(32.2%)	0.000	276(84.7%)	50(15.3%)	0.000
	Yes	249	116(46.6%)	133(53.4%)		156	76(48.7%)	80(51.3%)		106(67.9%)	50(32.1%)	

Notes: *preoperative CRP ≥5.15mg/L and postoperative CRP ≥72.45mg/L.

Table 3 Cox Regression Analysis of Factors Related to Survival in 482 Patients with Perioperative CRP

Criterion	PFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
Age(year) (≥ 51 vs <51)	1.260(0.972–1.633)	0.081	-	-	1.508(1.092–2.082)	0.013	1.076(0.772–1.500)	0.666
Histological type (Serous vs non-sereous)	2.916(2.032–4.184)	0	0.629(0.397–0.994)	0.047	2.039(1.367–3.042)	0	0.376(0.227–0.622)	0
Tumor grade (High-grade vs Low-grade)	3.785(2.416–5.932)	0	1.115(0.642–1.934)	0.7	2.763(1.668–4.576)	0	0.657(0.347–1.246)	0.199
FIGO stage(III–IV vs I–II)	9.132(5.972–13.966)	0	7.820(4.608–13.270)	0	10.465(5.800–18.883)	0	13.543(6.496–28.237)	0
Preoperative CA125 (U/mL) (≥35 vs <35)	5.009(2.732–9.184)	0	1.705(0.865–3.361)	0.124	4.922(2.305–10.508)	0	2.067(0.882–4.842)	0.095
Postoperative residual tumor (cm) (≥1 vs <1)	3.655(2.761–2.837)	0	1.754(1.311–2.345)	0	4.610(3.340–6.362)	0	2.425(1.716–3.427)	0
Perioperative CRP (Both increased vs Other)	2.218(1.670–2.946)	0	1.510(1.124–2.028)	0.006	2.371(1.691–3.325)	0	1.580(1.109–2.251)	0.011

Table 4 Cox Regression Analysis of Factors Related to Survival in Early and Advanced Stage Subgroup of 482 Patients

Criterion		PFS				OS			
		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Early stage	Age (years)(≥ 51 vs <51)	1.787(0.794–4.025)	0.161	–	–	2.470(0.744–8.206)	0.140	–	–
	Histological type (Serous vs non-serous)	1.080(0.479–2.435)	0.853	-	-	0.334(0.073–1.534)	0.159	-	-
	Tumor grade (High-grade vs Low-grade)	1.676(0.733–3.830)	0.221	-	-	1.055(0.339–3.283)	0.926	-	-
	Preoperative CA125 (U/mL)(≥35 vs <35)	1.407(0.583–3.395)	0.447	-	-	1.203(0.362–3.995)	0.763	-	-
	Postoperative residual tumor (cm)(≥1 vs <1)	-	-	-	-	-	-	-	-
	Perioperative CRP (Both increased vs Other)	0.891(0.210–3.791)	0.876	-	-	0.043(0.000–297.045)	0.486	-	-
Advanced stage	Age (years)(≥ 51 vs <51)	0.929(0.706–1.222)	0.598	-	-	1.155(0.826–1.616)	0.399	-	-
	Histological type (Serous vs non-serous)	0.721(0.458–1.133)	0.156	-	-	0.515(0.321–0.828)	0.006	0.462(0.276–0.773)	0.003
	Tumor grade (High-grade vs Low-grade)	0.666(0.371–1.193)	0.172	-	-	0.428(0.231–0.793)	0.007	0.548(0.281–1.069)	0.078
	Preoperative CA125 (U/mL)(≥35 vs <35)	1.701(0.632–4.576)	0.293	-	-	1.469(0.468–4.615)	0.510	-	-
	Postoperative residual tumor (cm)(≥1 vs <1)	1.877(1.411–2.498)	0.000	1.766(1.321–2.360)	0.000	2.482(1.784–3.453)	0.000	2.539(1.803–3.575)	0.000
	Perioperative CRP (Both increased vs Other)	1.638(1.221–2.197)	0.001	1.495(1.109–2.016)	0.008	1.824(1.291–2.577)	0.001	1.587(1.108–2.271)	0.012

survival in 107 EOC patients.[24] Furthermore, the ratio of CRP and albumin has recently been suggested as a novel independent marker of poor prognosis among EOC.[28] Consistent with previous study, we found that preoperative CRP (≥5.15 mg/L) was an independent risk factor for survival in patients with EOC, in addition to the previous established prognosticators including FIGO stage and postoperative residual lesion.[11] KM analysis also revealed better prognosis in lower preoperative CRP. The potential cutoff values in different studies were varied, which might be due to the different cancer types and study population.

In accordance with the predictive value of preoperative CRP level, the present study firstly revealed significant relationships between the elevated perioperative CRP and advanced tumor stage, low grade, serous carcinoma, elevated preoperative serum CA125, chemotherapy resistance and surgical residue lesions. The relationship between CRP level and tumor stage in the present study supported the hypothesis that CRP production could be from

Table 5 Cox Regression Analysis of Factors Related to Survival in Serous and Non-Serous Stage Subgroup of 482 Patients

Criterion		PFS				OS			
		Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Non-serous	Age (years)(≥ 51 vs <51)	1.219(0.628–2.366)	0.558	-	-	1.250(0.610–2.564)	0.542	-	-
	FIGO stage (III–IV vs I–II)	11.171(5.616–22.219)	0.000	10.820(4.797–24.409)	0.000	13.267(6.149–28.622)	0.000	12.455(4.967–31.228)	0.000
	Tumor grade (High-grade vs Low-grade)	2.418(1.245–4.694)	0.009	0.776(0.358–1.679)	0.519	2.792(1.356–5.752)	0.005	0.670(0.280–1.602)	0.368
	Preoperative CA125 (U/mL) (≥35 vs <35)	4.201(1.629–10.836)	0.003	3.319(1.264–8.715)	0.015	4.576(1.596–13.119)	0.005	3.165(1.065–9.402)	0.038
	Postoperative residual tumor (cm)(≥1 vs <1)	8.124(3.101–21.278)	0.000	1.279(0.456–3.592)	0.640	10.489(3.948–27.868)	0.000	1.782(0.623–5.096)	0.281
	Perioperative CRP (Both increased vs Other)	2.208(0.916–5.324)	0.078	-	-	2.327(0.889–6.094)	0.085	-	-
Serous	Age (years)(≥ 51 vs <51)	1.205(0.909–1.599)	0.195	-	-	1.548(1.077–2.226)	0.018	1.078(0.741–1.568)	0.693
	FIGO stage (III–IV vs I–II)	8.627(4.561–16.318)	0.000	7.966(3.877–16.370)	0.000	22.459(5.553–90.836)	0.000	23.939(5.121–11.902)	0.000
	Tumor grade (High-grade vs Low-grade)	2.957(1.098–7.962)	0.032	1.960(0.713–5.386)	0.192	1.497(0.553–4.055)	0.427	-	-
	Preoperative CA125 (U/mL) (≥35 vs <35)	2.987(1.324–6.737)	0.008	0.519(0.208–1.297)	0.160	3.227(1.026–10.149)	0.045	0.283(0.079–1.015)	0.053
	Postoperative residual tumor (cm)(≥1 vs <1)	2.855(2.123–3.839)	0.000	1.827(1.347–2.478)	0.000	3.864(2.718–5.493)	0.000	2.492(1.717–3.615)	0.000
	Perioperative CRP (Both increased vs Other)	1.926(1.424–2.605)	0.000	1.599(1.166–2.192)	0.004	2.144(1.487–3.092)	0.000	1.613(1.107–2.350)	0.013

malignant cells.[20] As we know, tumor stage, grade and postoperative residual tumor are the most reliable predictors for clinical prognosis of EOC.[11,38,39] Thus, we speculated that perioperative CRP level could be adopted as a union factor to predict the prognosis of EOC.

As we anticipated, the levels of preoperative and postoperative serum CRP were both significantly higher in patients suffering chemoresistance, relapse and death than those in other patients. The relationship between CRP and chemoresistance suggested that increased perioperative CRP level could be used for selecting patients who would benefit from platinum-based chemotherapy. Moreover, Cox regression analysis revealed higher perioperative CRP (both preoperative ≥5.15 mg/L and postoperative ≥72.45 mg/L) was an independent risk factor for recurrence and death of EOC in all enrolled patients. Further subgroup analysis according to tumor stage and histology confirmed similar results in advanced stage and serous EOC patients. KM analysis also revealed EOC patients with elevated perioperative CRP (both increased) suffered shorter PFS and OS. As an inflammatory factor, the elevated CRP in patients with poor prognosis proposed that anti-inflammatory therapy could be a potentially effective strategy for EOC treatment.[40]

Conclusions

In conclusion, as a study with a relatively larger sample size, we firstly validated that elevated perioperative CRP might serve as an independent prognostic predictor for EOC with shorter PFS and OS, especially in patients with advanced stage and serous EOC. The level of perioperative CRP could be an identifier to screen the potential effective strategy for clinical management of EOC. Nevertheless, due to the retrospective character of the present study, further prospective and experimental studies are warranted to verify the prognostic value of CRP and clarify the intrinsic mechanism of CRP in tumor progression.

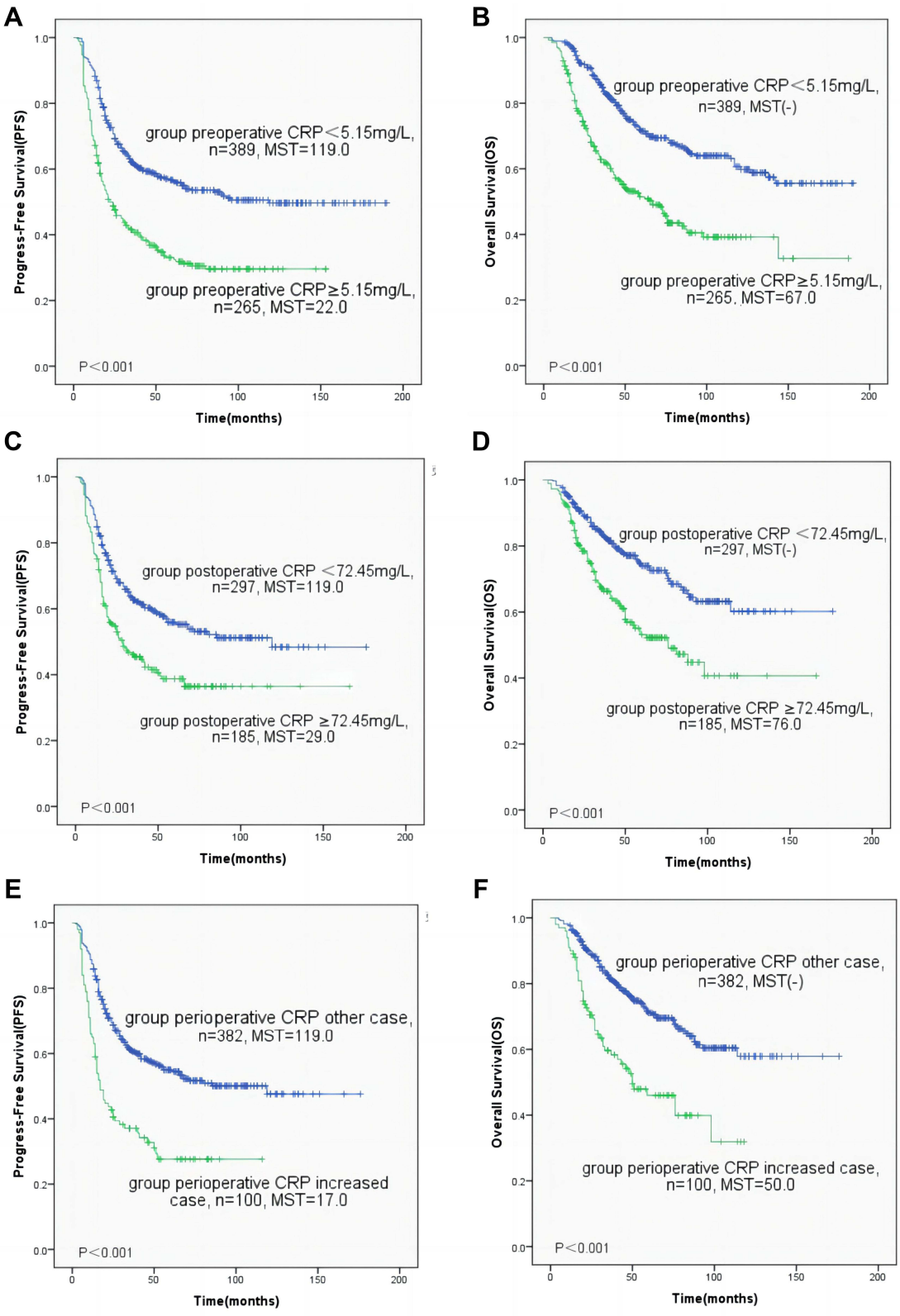

Figure 1 The relationship between perioperative CRP level and prognosis in EOC patients (**A**) Kaplan–Meier curves for PFS depending on the preoperative CRP level; (**B**) Kaplan–Meier curves for OS depending on the preoperative CRP level; (**C**) Kaplan–Meier curves for PFS depending on the postoperative CRP level; (**D**) Kaplan–Meier curves for OS depending on the postoperative CRP level; € Kaplan–Meier curves for PFS depending on the perioperative CRP level; (**F**) Kaplan–Meier curves for OS depending on the perioperative CRP level.

Abbreviations

CRP, C-reactive protein; EOC, epithelial ovarian carcinoma; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; MST, median survival time.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Approved by the Ethical Committee of women's hospital, Zhejiang University School of Medicine (IRB-20200230-R).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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