의학 석사 학위논문

수술 전 혈중 fibrinogen 수치의 상피성 난소암 예후 예측인자로서의 유용성에 대한 연구

CA-125 및 호중구/림프구 비율과의 비교

2017년 2월

서울대학교 대학원

의학과 산부인과학 전공

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Abstract

Preoperative levels of plasma fibrinogen as a predictor for stage, optimal debulking, and platinum-resistance in epithelial ovarian carcinoma

Comparison with CA-125 and neutrophil to lymphocyte ratio

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Objectives: This study was conducted to evaluate whether preoperative levels of fibrinogen, CA-125 and neutrophil to lymphocyte ratio (NLR) are predictive for FIGO stage, optimal debulking surgery and platinum resistance in epithelial ovarian cancer (EOC) patients.

Methods: Preoperative plasma levels of fibrinogen, CA-125 and neutrophil to lymphocyte ratio were retrospectively analyzed in patients with EOC who underwent primary cytoreductive surgery between January 2000 to December 2009. Clinico-pathologic characteristics including operative finding, FIGO stage, progression free interval after primary adjuvant chemotherapy and overall survival were evaluated. Response was evaluated with image using the RECIST criteria and serum CA-125 levels.

Results: Mean values of fibrinogen, CA-125 levels and NLR were significantly higher in patients with advanced FIGO stage and suboptimal debulking surgery. In advanced stage, suboptimal debulking surgery and high plasma fibrinogen levels correlated with platinum-resistance while CA-125 and NLR were statistically insignificant.

Receiver operating characteristic curve showed the best cutoff values of fibrinogen levels for the prediction for platinum resistance (504.5≥mg/dl, sensitivity: 64.4%, specificity: 69.6%, positive predictive value=0.71, negative predictive value=0.64).

In a log rank test, the high plasma fibrinogen levels and suboptimal debulking surgery showed poor prognosis for progression free interval and overall survival.

Conclusions: The preoperative fibrinogen levels are more useful to predict optimal debulking surgery and platinum resistance than CA-125 and NLR. The preoperative fibrinogen levels may be helpful to predict further prognosis.

Key words: Epithelial ovarian cancer, platinum resistance, fibrinogen, CA-125, neutrophil to lymphocyte ratio, debulking surgery

Student number: 2011-21843

Contents

List of tables

List of figures

I. Introduction

Epithelial ovarian cancer (EOC) is the most lethal malignancy in gynecologic cancer. It is estimated that 22,240 cases diagnosed and 14,030 deaths from EOC occur in the US in 2013. The cure rate of EOC is less than 40%. Although the improvement in surgical approach and various chemotherapeutic agent and target agents, EOC is still associated with the highest case-fatality ratio of all gynecologic cancers partly because of the propensity for the advanced-stage disease at clinical diagnosis [1]. The majority of advanced-stage patients relapses after initial response and ultimately dies of tumor recurrence. Given the high mortality and recurrence rate, it is critical to identify prognostic factors for EOC that can help the clinical decision.

Recently, several studies found plasma fibrinogen levels were shown as a useful prognostic factor for ovarian cancer and other solid tumors including gastric cancer, breast cancer, esophageal cancer, bladder cancer and recall cell carcinoma [2-7]. Fibrinogen interacting in multiple processes of coagulation cascade including platelet aggregation, clot formation, and wound healing, and angiogenesis [8]. These Fibrin, fibrinogen, and other coagulation factors' influence on cancer development, growth, and metastasis is evident [9], and these coagulation factors actively display a role in tumor cell growth, invasion, and metastasis by promoting tumor

neo-angiogenesis and by supporting the sustained adhesion of tumor cells [10].

On the other hand, many studies have demonstrated that various malignant tumor may be associated with systemic inflammation [11]. The inflammatory microenvironment of tumors actively influences proliferation, survival, and migration of tumor cells [9]. Fibrinogen represents one of the major acute phase proteins, and its biosynthesis increases with inflammation and stress [12]. Fibrinogen can directly bind to inflammatory or tumor cells, inducing synthesis of pro-inflammatory cytokines [13].

Despite these reports, fibrinogen measurement is not actively utilized in the clinic. Cancer antigen 125 (CA-125), most representative marker in EOC, is used to facilitate the diagnosis of EOC, to evaluate response to therapy and to detect recurrence. Neutrophil to lymphocyte ratio (NLR) is known as a prognostic factor for recurrence and death in patients with ovarian cancer [14, 15]. In this study, we tried to evaluate the usefulness of preoperative serum fibrinogen levels as a predictor for prognosis of EOC compared to CA-125 and NLR.

II. Materials and methods

After obtaining institutional review board approval, we retrospectively reviewed the medical records of patients treated for epithelial ovarian cancer at Seoul National University Hospital between January 1, 2000, and December 31, 2009. We included patients with the following inclusion criteria; those with histologically confirmed epithelial ovarian cancer, those who underwent primary staging operation with adjuvant taxane-platinum based chemotherapy, those with plasma fibrinogen, CA-125, complete blood count measured preoperatively within two weeks. We exclude patients with non-epithelial ovarian cancer, other malignant diseases, inflammatory diseases, coagulopathy, thromboembolism, anticoagulation medication, previous chemotherapy and radiation therapy.

Clinicopathologic characteristics including age, body mass index (BMI), FIGO stage, histology, surgical outcome, progression-free survival (PFS), overall survival (OS), response to chemotherapy, pre-operative levels of plasma fibrinogen, CA-125 and NLR. Optimal debulking surgery was defined when the size of the residual tumor was less than 1cm in the longest diameter and sub-optimal debulking surgery was defined when the size of the residual tumor was 1ᄎ or larger than 1cm in the longest diameter. PFS was defined as the time that elapsed from the date after primary surgery to

the date of clinically proven recurrence. OS was defined as the time that elapsed from the date of primary surgery to the date of death or last visit. Platinum resistance defined as disease progression in less than 6 months from last chemotherapy.

Statistical analyses were performed by SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL, USA). To evaluate preoperative fibrinogen levels as a predictor of EOC prognosis, we compared the correlation between the value of fibrinogen, CA-125 levels, and NLR to previous known prognostic factors including advanced stage, suboptimal surgical outcome, and resistance to platinum-based chemotherapy. After the test of normality with Kolmogorov-Smirnov test, continuous variables were compared using *t*-test and Mann-Whitney *U* test. Categorical variables were compared using the *Chi*-square and Fisher's exact test. Receiver operating characteristic (ROC) curve was used to determine the cutoff value of the fibrinogen level, NLR, and CA-125 level for predict optimal debulking surgery and platinum resistant disease. Furthermore, the sensitivity and specificity were compared by using the McNemar's test. Survival analyses were performed with Kaplan-Meier method with log-rank test and Cox's proportional hazard regression model with the hazard ratio (HR) and 95% confidence interval (CI). A *P* value of <0.05 was accepted as statistically significant.

III. Result

A total of 132 patients were enrolled in this study. Patient characteristics are shown in Table 1.

Mean age was 53.8 years (range, 27-81 years) and mean BMI was 23.5 (15.7-30.7). Fibrinogen levels were significantly higher in patients with advanced FIGO stage, sub-optimal surgery and platinum resistance disease CA-125 levels and LNR were high in advanced FIGO stage EOC and patients with residual disease. Though CA-125 levels were high in patient with serous carcinoma, there was no significant difference between platinum-sensitive and resistant patients (Table 2).

As all patients with early EOC underwent optimal debulking surgery and there was no platinum resistant disease in early stage EOC, further analyses were performed with advanced disease. Among 101 advanced EOC patients, 43 (42.6%) patients showed platinum resistant. Sub-optimal surgery, high fibrinogen levels, and NLR were associated with platinum resistance. There was no significant difference in age, BMI, histologic type and CA-125 levels between platinum-sensitive and resistant disease (Table 3).

Whether the fibrinogen, CA-125 levels, and NLR can predict the surgical outcome, and chemo response was evaluated with ROC curve (Figure 1). For predict surgical outcome, the cutoff value was found as 392.5 mg/dl for fibrinogen, 815.0U/ml for CA-125 and 3.2 for NLR. For these values, sensitivity was

determined as 80.7%, 63.2% and 64.9%, specificity as 47.7%, 45.5%, and 54.5%, and area under curve as 0.658 (P=0.007), 0.534 (P=0.554) and 0.577 (P=0.187), respectively. For platinum resistance, the cutoff value was found as 504.5 mg/dl for fibrinogen, 858.0 U/ml for CA-125 and 3.1 for NLR. For these values, sensitivity was determined as 69.8%, 53.5% and 72.1%, specificity as 75.9%, 39.7%, and 50.0%, and area under curve as 0.750 (P=0.000), 0.436 (P=0.275) and 0.602 (P=0.08), respectively. In McNemar' s test, fibrinogen, CA-125, and NLR show no difference in clinical outcome for the presence of postoperative residual tumor mass, only Fibrinogen shows no difference in clinical outcome for platinum resistance (Table 4).

In Cox regression survival analysis, tumor stage, surgical outcome, histologic type(serous and non-serous), age, fibrinogen, CA-125 levels and NLR were associated with disease-free and overall survival. However in multivariate analysis, fibrinogen, CA-125 levels were not associated with disease-free and overall survival (Table 5). Kaplan-Meier - curves for disease-free and overall survival by fibrinogen level are shown figure 2.

IV. Discussion

In this study, we can demonstrate that elevated fibrinogen levels are at substantially increased the risk for advanced disease, suboptimal surgical outcome, resistance to platinum-based chemotherapy and poor survival outcome.

To the date, the standard treatment of EOC is consist of debulking surgery and followed platinum taxane-based combination chemotherapy. The goal of surgical treatment is complete resection of all macroscopic disease at primary surgery. This has been shown to be the single most important independent prognostic factor in advanced EOC [16]. If optimal cytoreduction may not be achieved in primary debulking, neoadjuvant chemotherapy could be the alternative option [17, 18]. However, there are no specific criteria for selection of patient to abandon primary debulking surgery and underwent neoadjuvant chemotherapy, and various studies performed to establish the factors that most accurately predict the surgical outcome [19, 20]. Previous studies and our study, preoperative fibrinogen level reflects tumor burden and invasiveness [2, 5-7].

In our study, fibrinogen level has shown better statistical value than CA-125 and NLR to predict surgical outcome. Another usefulness of fibrinogen is availability. Fibrinogen is an established laboratory parameter that is used in daily clinical routine and is relatively cheap. Measurement of

fibrinogen levels could aid in preoperatively identifying a subgroup of patients that is at higher risk for the suboptimal surgical outcome.

Chemotherapy is another important treatment in EOC. Chemoresistant disease is another obstacle in the treatment of EOC. There is no precise explanation about how fibrinogen facilitates tumor to acquire chemoresistance. In our study, fibrinogen level has shown better statistical value than CA-125 and NLR to predict platinum resistance. As high fibrinogen level reflects tumor burden and more cancer tissue in patients, there is increased a risk of the resistant strain remain in residual mass. However in sub-analyses with patients underwent optimal surgery, high fibrinogen levels show correlation with platinum resistance as sub-optimal surgery group.

The molecular mechanisms underlying the relationship between high pretreatment plasma fibrinogen and worse survival of patients with solid tumors have not been fully elucidated. However, several experimental studies have shown that fibrinogen plays a critical role in tumor progression by inducing tumor cell proliferation, EMT, migration, angiogenesis, and hematogenous metastasis [7]. It has been demonstrated that fibrinogen binds directly to members of the transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF)

families, thus the fibrinogen/fibrin matrix acts as a reservoir for secreted growth factors that regulate tumor cell proliferation, inhibition of apoptosis, angiogenesis, and metastasis [21, 22]. Furthermore, it has been demonstrated that fibrinogen itself actively modulates the inflammatory process by inducing synthesis of pro-inflammatory cytokines from peripheral blood mononuclear cells and by interacting with leukocytes [5]. Platelet- fibrin microthrombi seem to act as a physical barrier preventing contact between natural killer cells and tumor cells, and thereby avoiding tumor cell elimination [11].

Though the association was not statistically significant in multivariate analysis, preoperative fibrinogen level associated with poor prognosis and critical clinic-pathological parameters in survival analysis as previous studies.

There are some limitations as follows. First, this study was retrospective design and single institutional study. Second, currently, many target agents are introduced to EOC treatment. Bevacizumab, an antiangiogenic agent, is most representative target agent and approved by FDA in the treatment of EOC. Bevacizumab is recommended not only for front-line treatment but recurrent cases. However, most patients enrolled in this study were not treated with these agents. As many target agents represent the effect by altering tumor microenvironment, the result may be different in

current treatment setting including target agents like bevacizumab.

In conclusion, this study suggests that preoperative fibrinogen reflect tumor burden to some extent and thus are predictive factors of treatment outcomes and that fibrinogen level could be regarded as a prognostic predictor in epithelial ovarian cancer patients.

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Table 1. Clinicopathologic characteristics of 132 patients

Parameter	No. of patients (%)
Age at diagnosis (mean±SD, year)	53.8±11.2
Body mass index (mean±SD, kg/m^2)	23.5±3.0
Histological type	
Serous	87 (65.9)
Endometrioid	22 (16.7)
Clear cell	13 (9.8)
Mucinous	7 (5.3)
Other	3 (2.3)
FIGO stage	
I	22 (16.7)
II	9 (6.8)
III	85 (64.4)
IV	16 (12.1)
CA-125 (mean±SD, U/ml)	4544.9±26290.9
Fibrinogen (mean±SD, mg/dl)	473.1±147.2
Neutrophil to lymphocyte ratio	4.0±2.5
Surgical outcome	
Optimal	75 (56.8)
Sub-optimal	57 (43.2)
Response to platinum chemotherapy	
Sensitive	89 (67.4)
Resistant	43 (32.6)
Progression free survival (median, month)	18.5
Overall survival (median, month)	62.5

FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation

Table 2. Differences of Fibrinogen, CA-125 levels and neutrophil to lymphocyte ratio (NLR) according to patient characteristics

Parameter	mean±SD					
	Fibrinogen (mg/dl)	*p*	CA-125 (U/ml)	*p*	NLR	*p*
Histological type						
Serous	484.8±140.9	.159	6187.3±32265.8	.001	4.3±2.7	.132
Non-serous	450.3±157.8		1369.7±2728.8		3.5±1.9	
FIGO stage						
I, II	409.6±126.7	.007	1044.8±1976.0	.000	3.1±1.8	.006
III, IV	498.5±148.1		5619.2±29989.2		4.3±2.6	
Surgical outcome						
Optimal	436.3±148.5	.000	1788.7±3413.6	.023	3.6±2.4	.012
Sub-optimal	521.5±131.7		8171.5±39723.9		4.5±2.5	
Response to platinum chemotherapy						
Sensitive	427.4±123.6	.000	2148.3±3556.2	.595	3.6±2.2	.008
Resistant	567.6±148.3		9505.3±45739.1		4.8±2.8	

FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation; NLR, neutrophil to lymphocyte ratio

Table 3. Comparison of clinicopathologic characteristics according to platinum responsive in advanced epithelial ovarian carcinoma patients.

Parameter	No. or mean±SD		p
	Platinum sensitive (n=58)	Platinum resistant (n=43)	
Age	56.1±10.5	55.3±9.6	.773
Body mass index	23.9±2.9	23.1±3.0	.183
Histological type			
Serous	46	31	.271
Non-serous	12	12	
Surgical outcome			
Optimal	32	12	.005
Sub-optimal	26	31	
Fibrinogen (mg/dl)	436.9±121.9	567.6±148.3	.000
CA-125 (U/ml)	2738.2±4056.2	9505.3±45739.1	.275
Neutrophil to lymphocyte ratio	3.9±2.4	4.8±2.8	.080

SD, standard deviation

Table 4. Receiver operating characteristic coordinates and diagnostic measures of plasma fibrinogen, CA-125 levels and neutrophil to lymphocyte ratio (NLR) to predict surgical out come and platinum resistance.

(A) Residual mass ≥1cm

	AUC	p	Cutoff	Sensitivity	Specificity	PPV	NPV	ACC	p (McNemar's test)
Fibrinogen	0.658	0.007	392.5	80.7	47.7	66.7	65.6	66.3	0.58
CA-125	0.534	0.554	815.0	63.2	45.5	60.0	48.8	53.4	0.77
NLR	0.577	0.189	3.2	64.9	54.5	64.9	54.5	57.7	0.50

(B) Platinum resistance

	AUC	p	Cutoff	Sensitivity	Specificity	PPV	NPV	ACC	p (McNemar's test)
Fibrinogen	0.750	0.000	504.5	69.8	75.9	68.2	77.2	73.3	0.23
CA-125	0.436	0.275	858.0	53.5	39.7	39.7	53.6	45.5	0.003
NLR	0.602	0.08	3.1	72.1	50.0	51.7	70.7	59.4	<0.001

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; NLR, neutrophil to lymphocyte ratio

Table 5. Univariate analysis of clinicopathologic factors affecting progression-free survival and overall survival in epithelial ovarian carcinoma patients

	Progression free survival		Overall survival	
	p-value	HR (95% CI)	p-value	HR (95% CI)
Age	0.001	1.03(1.01-1.05)	<0.001	1.05(1.03-1.07)
Body mass index	0.943	0.998(0.93-1.07)	.796	1.01(0.94-1.09)
Advanced stage	<.001	7.24(3.3-15.7)	0.000	10.18(3.70-28.04)
Serous type	0.009	1.85(1.16-2.95)	0.008	2.064(1.212-3.517)
optimal surgery	.000	0.24(0.16-0.38)	0.000	.290(0.18-0.47)
Platinum resistance	.000	17.10(9.96-29.35)	0.00	7.05 (4.37-11.36)
Fibrinogen level >504.5 mg/dl	0.003	1.89 (1.25-2.87)	0.003	2.02(1.28-3.19)
Serum CA-125 > 858.0U/ml	0.216	1.30(0.86-1.97)	0.784	1.066(0.677-1.678)
Neutrophil to lymphocyte ratio >3.1	0.042	1.55(1.02-2.37)	0.033	1.67(1.04-2.67)

HR, hazard ration; CI, confidential intervial

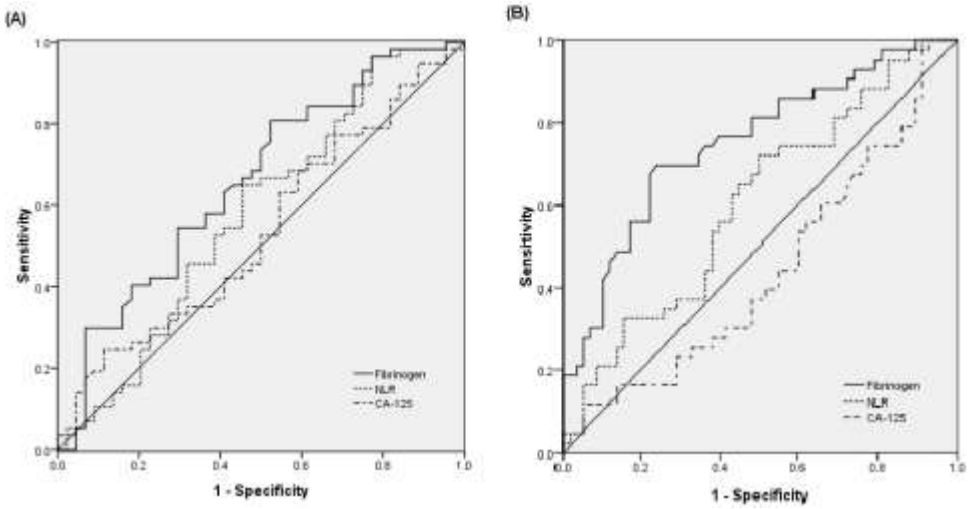

Figure 1. Receiver operating characteristic curves of plasma fibrinogen, CA-125 levels, and neutrophil to lymphocyte ratio for sub-optimal surgery (A), and platinum resistance (B)

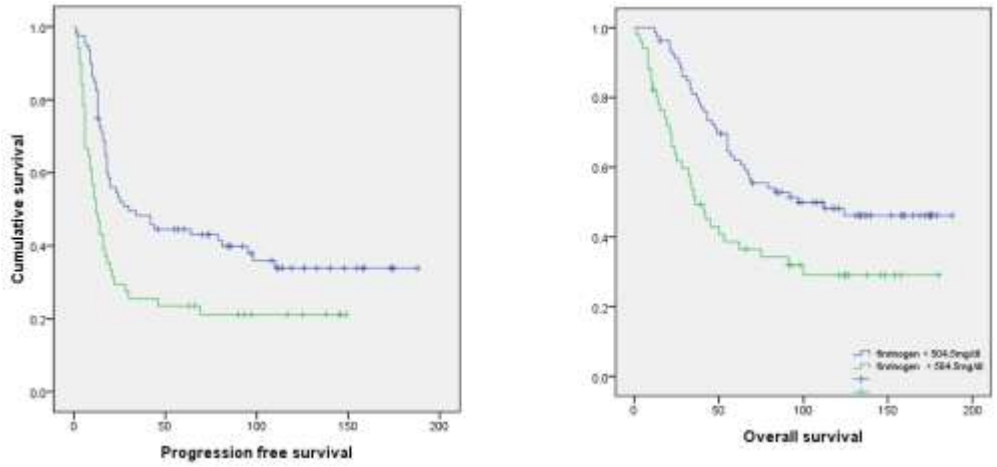

Figure 2. Kaplan-Meier curves for progression free survival and overall survival according fibrinogen levels (cutoff 504.5mg/dl)

국문 초록

수술전 혈중 fibrinogen 수치의 난소암 예후 예측인자로서의 유용성에 대한 연구

CA125 및 호중구/림프구 비율과의 비교

서울대학교 대학원

의학과 산부인과학 전공

성중엽

목적: 수술 전 혈중 fibrinogen 수치가 상피성 난소암의 병기, 최적의 종양 감축술 시행 여부 및 백금계 항암제 저항성과 같은 상피성 난소암의 예후인자를 예측하는데 유용한지를 알아보고자 하였다.

방법: 상피성 난소암으로 일차 종양감축술을 시행한 148명의 환자를 대상으로 후향적 의무기록 분석을 통해 자료를 수집하였다. 수술 소견 및 FIGO 병기, Taxane 및 platinum 항암제에 대한 반응에 따라, 초기 난소암과 진행성 난소암, 최적 종양감축술 시행여부, 백금계 항암제

저항성에 따라 그룹을 나누었다. 각 그룹의 수술전 혈중 fibrinogen 수치, CA125 수치 및 호중구/림프구 비율을 조사하여 이를 비교 분석하였다.

결과: 수술 전 혈중 fibrinogen, CA-125 호중구/림프구 비율의 평균치는 진행성 난소암과 수술 후 잔류종양이 남은 그룹에서 유의하게 높게 측정되었다. 진행성 난소암의 경우, 수술 후 잔류종양의 여부 및 백금계 항암제에 대한 저항성은 수술 전 혈중 fibrinogen 수치와 통계적으로 유의한 상관관계를 보였다.

항암제 저항성을 구분하기 위한 혈중 fibrinogen 수치를 Receiver operating characteristic curve를 이용하여 구하였고, 절단값 504.5mg/dl로, 민감도는 64.4%, 특이도는 69.6%, 양성 예측률은 0.71, 음성 예측률은 0.64였다. 높은 수술전 fibrinogen 수치는 무진행 생존기간과 전체 생존기관에 불량한 영향을 주고 있음을 확인하였다.

결론: 수술전 높은 혈중 fibrinogen 수치는 진행성 난소암의 불량한 예후 인자이며, 이는 난소암의 예후와 관련한 최적 종양감축술 여부와 항암제 저항성을 예측하는데, CA 125나 호중구/림프구 비율보다 우수하였다.

주요어: 상피성 난소암, 피브리노겐, CA-125, 호중구/림프구 비율, 항암제 저항성, 종양감축술

학번: 2011-21843