RESEARCH ARTICLE

Impact of Prognostic Factors on Survival Rates in Patients with Ovarian Carcinoma

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Abstract

Purpose: The aim of the present study was to invesitigate the impact of significant clinico-pathological prognostic factors on survival rates and to identify factors predictive of poor outcome in patients with ovarian carcinoma. Materials and Methods: A retrospective chart review of 74 women with pathologically proven ovarian carcinoma who were treated between January 2006 and April 2011 was performed. Patients were investigated with respect to survival to find the possible effects of age, gravida, parity, menstruel condition, pre-operative Ca-125, treatment period, cytologic washings, presence of ascites, tumor histology, stage and grade, maximal tumor diameter, adjuvan chemotherapy and cytoreductive success. Also 55 ovarian carcinoma patients were investigated with respect to prognostic factors for early 2-year survival. Results: The two-year survival rate was 69% and the 5-year survival rate was 25.5% for the whole study population. Significant factors for 2-year survival were preoperative CA-125 level, malignant cytology and FIGO clinical stage. Significant factors for 5-year survival were age, preoperative CA-125 level, residual tumor, lymph node metastases, histologic type of tumor, malignant cytology and FIGO clinical stage. Logistic regression revealed that independent prognostic factors of 5-year survival were patient age, lymph node metastasis and malignant cytology. Conclusions: We consider quality registries with prospectively collected data to be one important tool in monitoring treatment effects in population-based cancer research.

Keywords: Ovarian cancer - prognostic factors - survival analysis - Turkey

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Introduction

Ovarian carcinoma (OC) is the fourth most common cause of cancer-related death in women, but is the most lethal of the gynaecological malignancies (Sankaranarayanan, 2006). Seventy-five percent of women with OC present with an advanced disease at the time of diagnosis, and the 5-year survival ratio from OC is less than 50% worldwide. Epithelial ovarian tumors constitute the majority (90%) of ovarian malignancies (Gertig et al., 2002). Approximately 85% of epithelial ovarian tumors are invasive, while 15% are borderline ovarian tumors (Riman et al., 1998). To date, no firm conclusion can be drawn about the etiology of OC (Riman et al., 2004).

Prognostic factors can help identify subgroups of patients with especially poor prognosis and alert us to the need to develop alternative treatment strategies for these patients, while in clinical trials prognostic factors are used to balance patients between treatment arms to minimise the risk of confounding. Many studies have evaluated the survival of epithelial OC and its relation to established and proposed prognostic variables. In general, these studies have shown a poor long-term survival (Clark et al., 2001). Patient's age, residual disease after primary surgery, histological type and grade of tumor, and advanced stage are generally accepted as poor prognostic factors. However, the prognostic significance of some of the readily available clinical and pathological factors such as parity, preoperative serum carbohydrate antigen 125 (CA-125) levels, and lymph node metastases, has been debated (Bosze et al., 2000; Heintz et al., 2006).

The aim of the present study was to investigate the impact of significant clinico-pathological prognostic factors on survival time and to identify factors predictive of poor outcome in patients with OC.

Materials and Methods

Study Design: Ethical approval to perform the study was obtained from the ethical committee of our institute. A retrospective study was performed on 74 women with pathologically proven OC who were treated between January 2006 and April 2011 was performed. 5-year survival rates for the whole study group and 2-year

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survival rates for 55 OC patients followed for more than 24 months were investigated with respect to prognostic factors. Disease stage was determined according to the International Federation of Gynecologists and Obstetricians (FIGO) staging scheme (FIGO, 1987), and clinical determination was based on extensive surgical and cytological assessment. Cases with metastatic tumors, borderline tumors, serous cancers of serous surfaces, malignant mesenchymal tumors, and other carcinomas which were operated with initial diagnoses of ovarian cancer were not included in the study. Besides, patients who received neo-adjuvant chemotherapy, adjuvant radiotherapy or underwent interval debulking were excluded from the study. In line with the inclusion criteria 74 patients who received standard therapy were evaluated.

Outcome Parameters: The studied parameters were age at diagnosis, gravida, parity, menstruel condition, thrombocyte count, serum CA-125 levels, type of surgery, amount of residual tumor at the end of surgery, lymph node metastasis, tumor histology (grade and type), clinical stage (FİGO), cytologic washings, and adjuvant chemotherapy. The follow-up was the time from the end of initial treatment to death or to the last medical visit. Also 55 OC patients were investigated with respect to prognostic factors for early 2-year survival. Dependent variables were 5-year survival rates (%) and median survivals (years). Independent variables were patient's age, number of pregnancies, parities, menopausal status (premenopausal vs. postmenopausal), preoperative Ca-125 value, peritoneal cytology, tumoral stage, grade and cytoreductive success rate.

Statistical Analysis: Data were analyzed using the Statistical Package for Social Sciences 11.0 for Windows (SPSS Inc., Chicago, IL). The results for all items were expressed as mean±SD, assessed within a 95% reliance and at a level of $p<0.05$ significance. Numeric data and percentages related to patient's features, and prognostic characteristics, necessary cross comparisons were presented as descriptive statistics. A univariate non-parametric analytical method and chi-square test examined the correlation between prognostic factors, and survival rates. Survival curves were estimated using the Kaplan-Meier method. A univariate analysis of potential prognostic factors was performed with the log-rank test for categorical factors and with the univariate Cox analysis for continuous variables. Parameters with a p value <0.15 at the univariate step were included in the multivariate regression Cox proportional hazards model.

Results

This study was comprised of 74 patients. The mean age of the study group was 57.0±12.7 (range 32-80) years. Demographic, clinical, preoperative and postoperative variables of the patients were shown in Table 1. A considerable majority (63.5%) of patients referred with complaints of abdominal pain, and other presenting complaints like abdominal distension (27%), postmenopausal bleeding (4.1%) and other symptoms (5.4%). Median preoperative CA-125 value of 769 (range 4.9 to 828) mU/L, and platelet counts of 391 (range 198 to 979) $\times 10^3$ Ku/dl were determined. In 36 out of 72 patients who underwent lymph node dissections, metastatic lymph nodes were detected, while in remaining 36 patients lymph node metastases were not encountered. Pelvic lymph node metastases were detected in 23 patients, while 21 patients had para-aortic lymph metastases. Both pelvic and para-aortic involvements were observed in 20 patients. Median follow-up period for 74 patients was 23.5 months and 35 of them (47.3%) died, while 39 (%52.7) patients are still monitored. Fifty-five patients were reportedly monitored at least 2 years, 17 of them (30.9%) died, and 38 (69.1%) of them survived.

The impact of the variables related to the patient, and the disease on 2-, and 5 year-survivals is evaluated in Table 2. Age-related survival curve was shown in Figure 1. Patient's age of ≥50 had no effect on 2-year survival, while it had negative effect on 5-year survival (p=0.003).

Table 1. Patient Characteristics

Variable		n (%)
Age (years)	<50	23 (31.1%)
	≥50	51 (68.9%)
Parity	Nulliparity	4 (5.4%)
	Multiparity	70 (94.6%)
Reproductive period	Premenopausal	26 (35.1%)
	Postmenopausal	48 (64.9%)
Infertility	Present	4 (5.4%)
	Absent	70 (94.6%)
Surgery	Primary cytoreductive surgery	63 (85.1%)
	Second debulking for recurrence	11 (14.9%)
Residual tumor	<1cm	27 (36.5%)
	≥1cm	47 (63.5%)
Blood transfusion	Absent	32 (43.2%)
	Present	42 (56.8%)
Histologic grade	Grade 1	10 (13%)
	Grade 2	13 (41.9%)
	Grade 3	33 (44.6%)
Histological type	Serous	39 (52.7%)
	Mixed	9 (12.2%)
	Endometrial	8 (10.8%)
	Clear cell	7 (9.5%)
	Mucinous	6 (8.1%)
	Brenner tumor	3 (4.1%)
	Undifferentiated	1 (1.4%)
Clinical stage (FIGO)	Stage I	21 (28.4%)
	Stage II	4 (5.4%)
	Stage III	42 (56.8%)
	Stage IV	7 (9.5%)
Malignant cytology	Absent	31 (41.9%)
	Present	43 (58.2%)
Adjuvant chemotherapy	Absent	24 (32.4%)
	Present (Platinum sensitive)	26 (35.1%)
	Present (Platinum resistant)	24 (32.4%)
Status	Exitus	35 (47.3%)
	Alive	39 (52.7%)

Demographic, clinical, pre- and postoperative variables of the patients

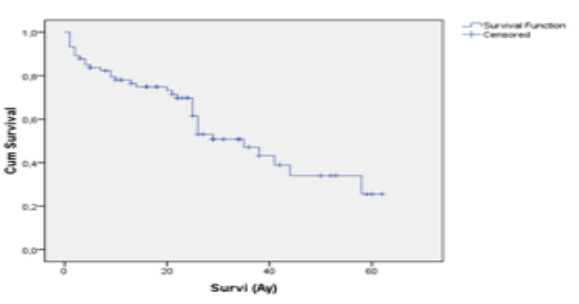

Figure 1. Five-year Survival Curve of the Study Group

Table 2. Correlation between Prognostic Characteristics and 2-, and 5-year Survival Rates

		2-years survival				5-years survival			
		Exitus n (%)	Alive n (%)	Total	p value	Exitus n (%)	Alive n (%)	Total	p value
Age (years)	<50	5 (26.32%)	14 (73.68%)	19	0.592	5 (21.7%)	18 (78.3%)	23	0.003
	≥50	12 (33.33%)	24 (66.67%)	36		30 (58.8%)	21 (41.2%)	51	
	Total	17 (30.91%)	38 (69.09%)	55		35 (47.3%)	39 (52.7%)	74	
Thrombocyte count	<400	11 (36.67%)	19 (63.33%)	30	0.311	18 (40.9%)	26 (59.1%)	44	0.183
	≥400	6 (24.00%)	19 (76.00%)	25		17 (56.7%)	13 (43.3%)	30	
	Total	17 (30.91%)	38 (69.09%)	55		35 (47.3%)	39 (52.7%)	74	
CA 125	<35	-	10 (100%)	10	NC	1 (7.1%)	13 (92.9%)	14	0.004
	35-500	13 (44.83%)	16 (55.17%)	29		21 (55.3%)	17 (44.7%	38	
	>500	4 (25.00%)	12 (75.00%)	16		13 (59.1%)	9 (40.9%)	22	
	Total	17 (30.91%)	38 (69.09%)	55		35 (47.3%)	39 (52.7%)	74	
Residual tumor	<1cm	8 (22.86%)	27 (77.14%)	35	0.087	6 (22.2%)	21 (77.8%)	27	0.001
	≥1cm	9 (45.00%)	11 (55.00%)	20		29 (61.7%)	18 (38.3%)	47	
	Total	17 (30.91%)	38 (69.09%)	55		35 (47.3%)	39 (52.7%)	74	
Lymph node metastasis	Absent	5 (17.86%)	23 (82.14%)	28	0.089	11 (30.6%)	25 (69.4%)	36	0.005
	Present	8 (40.00%)	12 (60.00%)	20		23 (63.9%)	13 (36.1%)	36	
	Total	13 (27.08%)	35 (72.92%)	48		34 (47.2%)	38 (52.8%)	72	
Histologic grade	Grade 1	1 (16.67%)	5 (83.33%)	6	NC	19 (57.6%)	14 (42.4%)	33	0.108
	Grade 2	8 (32.00%)	17 (68.00%)	25		14 (45.2%)	17 (54.8%)	31	
	Grade 3	8 (33.33%)	16 (66.67%)	24		2 (20%)	8 (80%)	10	
	Total	17 (30.91%)	38 (69.09%)	55		13 (52%)	12 (48%)	25	
Histological type	Serous	11 (39.29%)	17 (60.71%)	28	0.171	22 (56.4%)	17 (43.6%)	39	0.071
	Non- serous	6 (22.22%)	21 (77.78%)	27		12 (35.3%)	22 (64.7%)	34	
	Total	17 (30.91%)	38 (69.09%)	55		34 (46.6%)	39 (53.4%)	73	
Malignant cytology	Absent	4 (16.67%)	20 (83.33%)	24	0.023	11 (35.5%)	20 (64.5%)	31	0.067
	Present	13 (46.43%)	15 (53.57%)	28		24 (57.1%)	18 (42.9%)	42	
	Total	17 (32.69%)	35 (67.31%)	52		35 (47.9%)	38 (52.1%)	73	
Clinical stage (FIGO)	Early stage (I&II)	2 (10.53%)	17 (89.47%)	19	0.017	6 (24%)	19 (76%)	25	0.004
	Late stage (III&IV)	15 (41.67%)	21 (58.33%)	36		29 (59.2%)	20 (40.8%)	49	
	Total	17 (30.91%)	38 (69.09%)	55		35 (47.3%)	39 (52.7%)	74	

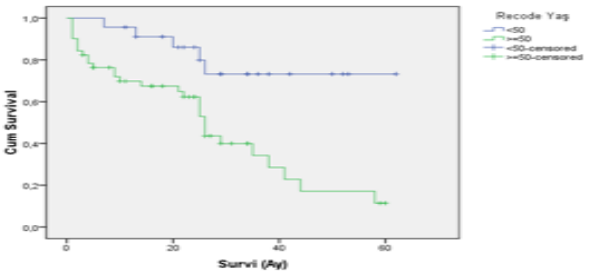

Figure 2. Survival Curve of Patients for Patient's Age

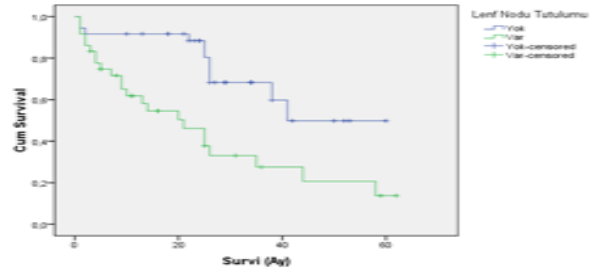

Figure 3. Survival Curve of Patients for Lymph Node Metastasis

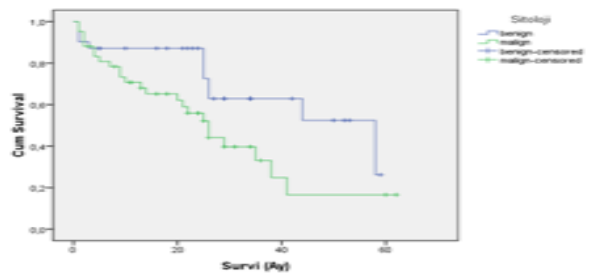

Figure 4. Survival Curve of Patients for Malignant Peritoneal Cytology

The survival curve of patients for patient's age was shown in Figure 2. The effect of preoperative CA-125 level on 2-year survival was not significant, while it was negatively correlated with 5-year survival rates, in other words 5-year survival rates increased as CA-125 levels decreased (p=0.004). Although residual tumor burden did not exert a significant effect on 2-year survival, tumor burden of >1 cm seemed to be related to 5-year survival (p=0.001). The presence of lymph node involvement did not affect 2-year survival, but it demonstrated an unfavorable effect on 2-year survival (p=0.005). Survival curve of patients for lymph node metastasis was shown in Figure 3. Presence of malignant cytology demonstrated an adverse effect on 2-year survival (p=0.023) while it did not create a significant change on 5-year survival rates. FIGO stage seemed to be adversely correlated with both 2-, and 5-year survivals (p=0.017 and 0.004, respectively). Survival curve of patients for malignant peritoneal cytology was shown in Figure 4. Any statistically significant effects of preoperative platelet counts, postoperative histologic type, and degree of differentiation on 2-, and 5-year survivals have not been revealed.

In Table 3, potential prognostic factors effecting survival were evaluated by univariate analysis, based on median survival time within 95%CI. Since for all variables, median 2-year survival time was higher than the mean values, it was not calculated. When overall population was taken all together, 2- year survival rate was determined as 69 percent. However median 5-year survival time was 35 months, and 5-year overall survival rate was estimated as 25.5 percent. In patients with ≥50 years of age, 5-year median survival time was 26 months

Table 3. Prognostic Factors Affecting Survival Rates

			2-years survival				5-years survival		
		Median survival (months) median±SD	2-years survival (%)	Std. error	Logrank p value	Median survival (months) median±SD	5-years survival (%)	Std. error	Logrank p value
Total		-	69%	6.3%	-	35±5.099	25.5%	9.7%	
Age (years)	<50	-	73.7%	10.1%	0.508	-	73.2%	10.5%	0.002
	≥50	-	66.4%	7.9%		26±1.736	11.4% (51)	7.2%	
Thrombocyte count	<400	-	63%	8.9%	0.315	41±11.9	27.8% (52)	13.9%	0.853
	≥400	-	76%	8.5%		26±7.056	28.2%	11.3%	
CA 125	<35	-	-	-	0.027	-	66.7% (52)	27.2%	0.005
	35-500	-	54.8%	9.3%		26±1.722	13.5% (59)	10.8%	
	>500	-	75%	10.8%		25±3.058	22.3%	12.2%	
Residual tumor	<1cm	-	76.9%	7.2%	0.082	-	56%	16.3%	<0.001
	≥1cm	-	55%	11.1%		25±1.598	13.1%	7.8%	
Lymph node metastasis	Absent	-	82%	7.3%	0.101	41±---	49.8%	13%	0.001
	Present	-	60%	11%		21±5.448	13.8%	8.3%	
Histologic grade	Grade 1	-	83.3%	15.2%	0.759	26±3.539	11.0% (59)	9.3%	0.155
	Grade 2	-	68%	9.3%		26±7.196	34.8%	13%	
	Grade 3	-	66.2%	9.8%		-	80%	12.6%	
Histological type	Serous	-	60.7%	9.2%	0.177	26±0.678	18.3%	10.4%	0.021
	Non- serous	-	77.4%	8.1%		58±12.872	25.5%	19%	
Malignant cytology	Absent	-	83.3%	7.6%	0.033	58±17.097	26.2% (59)	19.6%	0.025
	Present	-	53.6%	9.4%		26±3.012	16.5%	9.6%	
Clinical stage (FIGO)	Early stage (I&II)	-	89.5%	7%	0.031	-	55.7%	16.2%	0.001
	Late stage (III&IV)	-	58.3%	8.2%		25±1.559	13.5%	8%	

and survival rate was 11.4 percent. Since 5-year survival rate was above median values i.e. 73.2%, advanced age was accepted as an unfavorable prognostic marker for survival (p=0.002).

When the contribution of preoperative CA-125 levels on survival is evaluated, in patients with CA-125 values in the range of 35-500 mU/L, median 5-year survival was 26 months while 59-month survival rate was 13.5 percent. In patients with CA-125 levels of <35 mU/L median survival times were above the mean estimates, and 59-month survival rate was 66.7 percent. In the patient group with CA-125 values of ≥500, both 2-, and 5-year survival rates were detected to be at significantly higher levels when compared with cases whose CA-125 values were in the range of 35-500 mU/L. In patients with residual tumor burden ≥1 cm, 5-year survival was 25 months, and survival rate was estimated to be 13.1 percent. However in patients with residual tumor burden of <1 cm, 5-year survival rate was 56%, with a highly significant intergroup difference (p<0.001). In patients without lymph node involvement, median 5-year survival time was 41 months, and overall survival, 49.8 percent. Five-year median survival time of patients with lymph node involvement was 21 months, and survival rate, 13 percent with a statistically significant intergroup difference (p=0.001). In subgroup analysis of histologic types as serous and nonserous groups, median 5-year survival in serous type was 26 months, and survival rate, 18.3%, and for nonserous type median 5-year survival was 55 months, and survival rate, 25.5%. In this analysis, serous subtype appears to be an indicator of unfavorable prognosis (p=0.021). In cytologic examination, 2-year survival rate of the patient group with a benign cytology was 83.3%, while median 5-year survival time was 58 months, 5-year survival rate, 26.2 percent. In patients with malignant cytology, 2-year survival rate was 53.6%, while median 5-year survival time and survival rate were 26 months, and 16.5%, respectively. Malignant cytology appears to be an unfavorable indicator of both 2-, and 5-year survival (p=0.033 and p=0.025, respectively). In evaluation of FIGO clinical stages, in patients with advanced disease median 5-year survival time was 25 months, and survival rate, 13.5%, while for early stage disease survival rate was higher than the median value (57.7%) with a statistically significant intergroup difference (p=0.001).

Table 4. Prognostic Factors Affecting 5 Year Survival

	p value	Risk	95%CI
Age (years)	0.012	3,446	1.318-9.012
Lymph node metastasis	0.007	2,754	1.320-5.744
Malignant cytology	0.042	2,189	1.030-4.649

In multivariate Cox regression analysis, age, lymph node involvement, and cytology were found to be statistically significant as prognostic factors influencing 5-year survival. When risk coefficients calculated according to the results of the analysis, mortality risk increased 3.44-fold in patients over 50 years of age, 2.75 times in the presence of lymph node involvement, and 2.2 times malignant cytology (Table 4).

Discussion

The aim of the present study was to invesitigate the impact of significant prognostic factors on survival rates and to identify factors predictive of poor outcome in patients with OC. A significant relationship was found between 2-year survival rate and preoperative CA-125 level, malignant cytology and FIGO clinical stage. Also, a significant relationship was found between 5-year survival rate and patient's age, preoperative CA-125 level, residual tumor, lymph node metastases, histologic type of tumor, malignant cytology and FIGO clinical stage. In a multivariate analysis independent prognostic factors of

5-year survival were patient's age, lymph node metastasis and malignant cytology.

A large study from the SEER program of the United States included more than 26,000 patients with non-clear cell OC tumors during a 14-year period (Chan et al., 2006). They showed a disease specific 5-year survival rate of 45.8% from the period 1993-1997. De Bois et al. reviewed the results of meta-analysis of 3 prospective randomized controlled studies encompassing 3126 patients with epithelial ovarian cancer, and found overall 5-year survival rate as 39%, and emphasized that this survival rate had been primarily affected by residual tumor burden, and consequently optimal surgery (du Bois et al., 2009). Gaemmoghami et al. prospectively randomized 186 patients into 2-year early survival (disease-free survival, and overall survival), and 5-year survival groups, and although they found similar 2-year survival rates, especially in the 5-year survival group, survival rates were 43% in those with surgical staging, and 38% in cases without surgical staging (without optimal debulking) (Gaemmaghami et al., 2011). In their review of epithelial ovarian cancer Green et al. indicated an average overall 5-year survival rate of 46 percent (Salzman J, et al, 2011). In the present study, when overall population was taken all together, 2- year survival rate was determined as 69 percent. However median 5-year survival time was 35 months, and 5-year overall survival rate was estimated as 25.5 percent.

Earlier studies on the prognostic significance of age in ovarian cancer have been inconclusive. Although most reports have shown that younger women are diagnosed with lower-stage and more well-differentiated tumors, and have an improved outcome compared with older women, others have found that age is not an independent prognostic factor after adjusting for stage and grade of disease (Chan et al., 2003; Chan et al., 2006). In addition, because of the low prevalence of young patients diagnosed with invasive ovarian cancer, these studies have also been limited by small numbers of patients, inclusion of low malignant potential tumors, germ cell or sex cord stromal tumors, and unstaged cancers. In a considerably larger population-based study from the SEER program of the United States, age was found to be a prognostic factor with a 5-year disease-specific survival rate of more than 78% in the group of very young patients (<30 years) (Chan et al., 2006). This survival advantage in favor of younger age groups persisted even after adjusting for stage, grade, and surgical treatment. Tang et al. retrospectively analyzed 71 patients aged <35 years, diagnosed as epithelial ovarian cancer, and advocated that in these patients frequently unilateral, lower grade tumors of serous subtype, with good prognosis, and an inclination for earlier identification were observed. They also asserted that all these characteristics had a favorable impact on prognosis. As independent prognostic factors tumoral differentiation (grade) and residual tumor burden have been demonstrated (Tang et al., 2008). In the research group of Moore et al., when 948 patients with epithelial ovarian cancer were screened as for prognostic factors, age appeared to be an important factor influencing treatment especially in advanced stage ovarian cancer, and the authors indicated that prognosis worsened with increasing age (Moore et al., 2004). In a 10-year long investigation, Tingulstad et al. evaluated independent and modifiable prognostic factors in 571 patients, and their data confirmed age as an independent prognostic factor (Tingulstad et al., 2003). Duration of ovulation more than 30 years is accepted as a risk factor for all histologic types. These characteristics were found to be especially associated with serous subtype. Matei et al. emphasized the duration of ovulation, and indicated parity as an important and favorable prognostic factor (Matei et al., 2010). Braem et al. asserted that the risk of ovarian cancer decreases in parous or hysterectomized women, and those with increased parity (Braem et al., 2010). In this current analysis of OC patients with long follow-up, younger age was an independent prognostic factor for improved survival. In the present study, the mean age of the study group was 57.0±12.7 years. Patient's age of ≥50 had no effect on 2-year survival, while it had negative effect on 5-year survival. In patients with ≥50 years of age, 5-year median survival time was 26 months and survival rate was 11.4 percent. Since 5-year survival rate was above median values i.e. 73.2%, advanced age was accepted as an unfavorable prognostic marker for survival.

Thrombocytosis is referred as an unfavorable prognostic factor in many cancer types. Thrombocytosis is frequently encountered especially in advanced stage cancers, and as a prognostic marker, it seems to be associated with increased tumor aggressivity (Gerestein et al., 2009). Li et al. indicated preoperative thrombocytosis and advanced stage as poor prognostic factors (Li et al., 2004). Gungor et al. described thrombosis as a negative prognostic factor, and detected its correlation with increased preoperative CA-125 levels, advanced stage, and shorter survival times (Gungor et al., 2009). CA-125 is the most frequently used marker of maximal sensitivity in the management of all stages of ovarian cancer. CA125 is expressed by over 80% of ovarian cancers, and levels at presentation correlate with the risk of malignancy, stage of disease and histology (Meyer et al., 2000). Controversies exist concerning the proper timing of CA-125 measurements and cutoff limits in its use as a prognostic factor for EOC. Several authors have found an independent prognostic value for preoperative CA-125 measurements, but this could not be confirmed in other reports (Cooper et al., 2002; Tingulstad et al., 2003; Duffy et al., 2005). According to Coussy et al., preoperative CA-125 values were apparently useful in determining appropriate method. They also aid in establishment of therapeutic strategy, guidance of optimal surgery, and improvement in overall and disease-free survival (Coussy et al., 2011). In the present study, the effect of preoperative CA-125 level on 2-year survival was not significant, while it was negatively correlated with 5-year survival rates, in other words 5-year survival rates increased as CA-125 levels decreased. When the contribution of preoperative CA-125 levels on survival is evaluated, in patients with CA-125 values in the range of 35-500 mU/L, median 5-year survival was 26 months while 59-month survival rate was 13.5 percent. In patients with CA-125 levels of <35 mU/L median survival times were above the mean estimates, and 59-month survival rate was

66.7 percent. In the patient group with CA-125 values of ≥500, both 2-, and 5-year survival rates were detected to be at significantly higher levels when compared with cases whose CA-125 values were in the range of 35-500 mU/L. This finding was tried to be explained with scarce number of patients with CA-125 levels of ≥500 in the patient population. In a study conducted by Wei-Na Wan et al, it was suggested that ovarian tumor tissue may have highly expressed ATAD2, which is associated with tumor stage, omentum-metastasis, ascites and CA-125. Increased ATAD2 may play important roles in tumor proliferation and migration. Expression of ATAD2 could serve in particular as a prognostic marker and a therapeutic target for ovarian cancer (Wan et al., 2014). Also it was found that increased expression of MMP- 9 was associated with poor prognosis in ovarian cancer patients. Down-regulation of MMP-9 is an attractive therapeutic approach which might improve outcome of ovarian cancer (Li et al., 2014). Those tumor markers might be researched in accordance with prognosis.

The importance of the residual tumor after surgery as a prognostic factor for survival in EOC patients was first acknowledged by Griffiths (Griffiths., 1975). He found a size of the residual tumor greater than 1.5 cm after debulking surgery to be related to a poor survival. Since then, there has been a debate concerning the size limit of the residual tumor after surgery and thereby the definition of optimal cytoreduction (Eisenkop et al., 2003). In a study by a Gynecologic Oncology Group of almost 300 patients with stage III EOC, a difference in survival was seen between those with a residual disease less than 2 cm compared with those who had 2 cm or greater tumor left (Hoskins et al., 1994). A study from the United States included 465 patients of stage IIIC between 1989 and 2003 and identified 3 groups with significantly different survival between the groups: no macroscopic disease, 1 cm or less residual tumor, and greater than 1 cm residual tumor (Chi et al., 2006). In a meta-analysis of 81 cohorts of almost 7000 stage III-IV EOC patients, a positive correlation was found between maximal cytoreduction and survival, with the extent of cytoreduction being the most powerful independent prognostic factor (Bristow et al., 2002). In the present study, although residual tumor burden did not exert a significant effect on 2-year survival, tumor burden of >1 cm seemed to be related to 5-year survival. In patients with residual tumor burden ≥1 cm, 5-year survival was 25 months, and survival rate was estimated to be 13.1 percent. However in patients with residual tumor burden of <1 cm, 5-year survival rate was 56%, with a highly significant intergroup difference.

Even though pelvic lymph node involvement is frequently observed in ovarian cancers, its pattern is variable, and it might be in the form of pelvic or para-aortic, bilateral, ipsilateral or contralateral involvement. In early stages systematic lymph node dissection has diagnostic and therapeutic roles. This is quite important for accurate diagnosis, and optimal surgical treatment (excision of possible micrometastatic foci and residual tumor burden of <1 cm) of patients with stage IIIC tumors. In advanced stages, correlated with increasing tumoral aggressivity, prognosis worsens in patients with lymph node involvement. Optimal debulking provides the highest opportunity for prolonged disease-free and overall survivals (Salet-Lizee, 2008). Abe et al. retrospectively evaluated the contribution of systematic lymphadenectomy on survival in 118, they underlined that systematic lymphadenectomy had improved disease-free, and overall survival in patients with disease confined in pelvis, however in cases with advanced stage who had had optimal debulking, systematic lympadenectomy had not influenced disease-free, and overall survivals. Although systematic lympadenectomy is beneficial for patients with clear cell carcinoma, in advanced stage patients who had had optimal debulking, systematic lympadenectomy did not further improve overall survival or disease-free survival in these patients (Abe et al., 2010). In a study conducted by Panici et al. with 419 stage III, and IV patients who had undergone systematic lympadenectomy or only bulky lymph node dissection, in patients with advanced stage optimal debulking, systematic lympadenectomy had not changed overall survival, but improved disease-free survival when compared with bulky node excision (Panici et al., 2005). In the present study, the presence of lymph node involvement did not affect 2-year survival, but it demonstrated an unfavorable effect on 2-year survival. Pelvic lymph node metastases were detected in 23 patients, while 21 patients had para-aortic lymph metastases. Both pelvic and para-aortic involvements were observed in 20 patients. In the present study, in patients without lymph node involvement, median 5-year survival time was 41 months, and overall survival, 49.8 percent. In patients with lymph node involvement median 5-year survival was 21 months, and survival rate, 13 percent.

The result of the present study found that grade and the histopathologic subtype of serous cystadenocarcinoma were of prognostic importance in the univariate analysis but not in the multivariate. Concerning grade and histopathologic subtypes of OC tumors, the results in other reports are conflicting. In an earlier population-based study from Sweden, grade was found to be an independent prognostic factor, but the prognostic importance of the histopathologic subtypes was dependent on stage, especially the mucinous tumors (Hogberg et al., 1993). Vergote et al. studied a group of 1545 patients with stage I disease and found that grade of disease was an independent prognostic factor associated with diseasefree survival (Vergote et al., 2001). In a study of OC patients from Norway from the 10-year period 1987-1996, no significance for either histopathologic subtype or grade could be shown (Tingulstad et al., 2003). In the present study, in subgroup analysis of histologic types as serous and nonserous groups, median 5-year survival in serous type was 26 months, and survival rate, 18.3%, and for non-serous type median 5-year survival was 55 months, and survival rate, 25.5%. In this analysis, serous subtype appears to be an indicator of unfavorable prognosis.

In this current analysis, malignant cytology was an independent prognostic factor for increased risk of recurrence and poorer survival. Early studies have demonstrated that patients with positive washing have a poorer prognosis (Keettel, 1958; Morton et al., 1961). Creasman et al. reported that 60% of 98 patients with

ovarian cancer who underwent surgery had abnormal peritoneal mcytologic specimens (Creasman, 1971). Likewise, a more recent report also found positive peritoneal washing cytology at initial surgery in 90 (80.4%) of 112 patients with ovarian carcinomas (Zuna, 1996). Those authors also showed that positive cytology portends a poorer prognosis. In the present study, presence of malignant cytology demonstrated an adverse effect on 2-year survival while it did not create a significant change on 5-year survival rates. In cytologic examination, 2-year survival rate of the patient group with a benign cytology was 83.3%, while median 5-year survival time was 58 months, 5-year survival rate, 26.2 percent. In patients with malignant cytology, 2-year survival rate was 53.6%, while median 5-year survival time and survival rate were 26 months, and 16.5%, respectively. Malignant cytology appears to be an unfavorable indicator of both 2-, and 5-year survival.

In a study conducted by Xiao-Hui Liu et al., the impact of season at the time of diagnosis was examined. It was found that only the recurrence season impacts the survival of epithelial ovarian cancer patients. However, the diagnosed season does not appear to exert a significant influence. In that study the other prognostic factors of epithelial ovarian cancer were age, clinical stage, pathological type, histological grade, residual disease after primary surgery and adjuvant chemotherapy cycles (Liu et al., 2014).

Previous studies have also demonstrated that stage of disease is a prognostic factor in early-stage ovarian cancers (Mizuno et al., 2003; Du Bois et al, 2005). It is clearly shown from the results of the present study that the survival is stage-dependent in the analysis of the study population. We found in the univariate analysis that FIGO stage was a powerful prognostic factor. It is essential to determine adjuvant treatment, and also accurate staging because of its marked effect on survival rates of the patients who were determined to be in the early stage of the disease by precise staging using optimal surgery are significantly different relative to advanced stages. Performance status of the patients in the early-stage of the disease is better because of diagnosis made at an earlier age. Therefore in these patients optimal surgical treatment can be achieved, and later they can tolerate adjuvant therapy well which all exert favorable effects on survival. In advanced stages, decreasingly suboptimal effect of surgery, and the presence of residual tumor burden which is one of the strongest prognostic factors affect survival unfavorably. In the present study, FIGO stage seemed to be adversely correlated with both 2-, and 5-year survivals. In evaluation of FIGO clinical stages, in patients with advanced disease median 5-year survival time was 25 months, and survival rate, 13.5%, while for early stage disease survival rate was higher than the median value (57.7%) with a statistically significant intergroup difference.

The advantage of our study is that we treated, and followed up all cases in our hospital with the same protocol. Multidisciplinary approach and a standard protocol were formulated. Their variables constitute characteristics of the patients' tumors. Disadvantage of the study is the presence of scarce number of patients in homogenous subgroups because of shorter follow-up period.

In summary, the present study of patients with OC showed that patient age at diagnosis, precence of lymph node metastasis and malignant cytology are of independent prognostic values. Mortality risk increased 3.44-fold in patients over 50 years of age, 2.75 times in the presence of lymph node involvement, and 2.2 times malignant cytology. In addition, a survival data, with a decline in the 2- to 5-year survival rate from 69% to 25.5%, were seen. We consider quality registries with prospectively collected data to be one important tool in monitoring treatment effects in population-based cancer research.

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