

Association between Stage and Degree of Differentiation with Ca-125 Levels and Inflammatory Response Markers in Malignant Serous Tumors of the Ovary

Keywords: Malignant serous ovarian tumors; Grade; Stage; Ca-125; NLR

Abstract

Objectives: The present study aimed to assess the association between stage and degree of differentiation (grade), and levels of Ca-125 and neutrophil-to-lymphocyte ratio (NLR), as an inflammatory marker, in serous ovarian carcinoma.

Materials and Methods: A total of 71 patients with serous ovarian carcinoma, who were operated between 2016 and 2020 at the Ankara Medicalpark Batikent Hospital, affiliated with the Yuksek Ihtisas University, were evaluated retrospectively. The retrospective evaluation included patients age, preoperative serum levels of Ca-125 and NLR. The patients were postoperatively staged based on the FIGO histopathological staging system and the degrees of differentiation as well as the status of lymph node involvement were recorded.

Results: The study participants had a mean age of 54.7 years, a mean Ca-125 level of 1199U/ml and a mean NLR of 5.8. The mean Ca-125 level was 331, 724, 1186 and 2134 in stage I, II, III and IV patients, respectively, indicating an increase in Ca-125 levels with the increasing stage ($p < 0.001$). The increased degree of differentiation (grade) was also significantly associated with Ca-125 levels. The higher the Ca-125 level, the higher the tumor grade ($p < 0.001$). The mean NLR was 3.28, 6.53, 6.73 and 6.76 in stage I, II, III and IV patients, respectively. There was an increase in NLR with increasing stage, and the difference was significant ($p = < 0.002$). No significant difference was found in NLR between grades 1 and 2, while there was a significant difference between grades 1 and 3 ($p < 0.001$).

Conclusion: The levels of Ca-125 and NLR were associated with an increased degree of differentiation and stage in epithelial malignant serous ovarian tumors.

Introduction

Ovarian cancer is the third most common cancer in women after cervical and uterine cancers. Nevertheless, it is associated with the highest mortality among gynecological cancers. Almost two-thirds of patients are diagnosed with the advanced stage. The 5-year overall survival in ovarian cancer is around 48%. The most common histopathological type in the epithelial ovarian cancer group is serous carcinoma. Prognosis varies by the sensitivity to chemotherapy. Serous carcinoma has a considerably high incidence of bilateral disease. The average age for diagnosis of epithelial ovarian tumors is 54 years [1,2].

There is currently no available screening test for ovarian tumors. Ca-125 and transvaginal ultrasonography are used for early diagnosis; however, no reduction has been observed in mortality rates in ovarian



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cancers after a 19-year follow-up with screening using the available diagnostic tools [3,4].

Ca-125 plays an important role in indicating the disease burden and as a follow-up criterion in the treatment of epithelial ovarian cancers. It has been recently suggested that systemic inflammatory response markers such as neutrophil-to-lymphocyte ratio (NLR) may be associated with clinical parameters in patients with epithelial ovarian carcinoma (EOC) [5-8]. In the present study, we aim to examine the association of CA-125 and NLR with stage and degree of differentiation in ovarian carcinoma.

Materials and Methods

This retrospective study included 71 patients with serous ovarian carcinoma who presented to the Yuksek Ihtisas University Ankara Medicalpark Hospital between 2016 and 2020. For all patients, preoperative levels of Ca-125 and hemogram parameters, postoperative lymph node involvement, the number of lymph nodes involved and degree of differentiation (tumor grade) based on the FIGO staging system were established.

The PASW Statistics (Version 18.0.Chicago: SPSS Inc.) software package was used for the statistical assessment. A Kolmogorov-Smirnov test was used for the differentiation of parametric and nonparametric variables, a one-way ANOVA was used to compare the means of multiple variables, and Tukel test was conducted for the comparison of post-hoc binary variable means. A p-value of less than 0.05 was accepted as statistically significant.

Results

The mean age of the study patients was 54.7 years; the mean Ca-125 and mean NLR were 1199 and 5.8, respectively; and lymph nodes were positive in 76.1% of patients. Among the patients, 14.1% were grade I, 15.5% were grade II and 70.4% were grade III, while 18.3% were stage I, 21.1% were stage II, 32.4% were stage III and 28.2% were stage IV (Table 1).

Table 1: General distribution mean of groups and parameters.

Parameter	Mean N(%)
Age	54.7 (25-82)
Ca 125	1199 (7-3742)
Neutrophil-to-lymphocyte ratio(NLR)	5.8 (1.63-12.83)
Number of Lymph Nodes	
No	17 (23.9%)
1-5	48(67.6%)
6-9	6 (%8.5)
Stage	
Stage 1	13 (18.3%)
Stage 2	15 (21.1%)
Stage 3	23 (32.4%)
Stage 4	20 (28.2%)
Grade	
Grade 1	10 (14.1%)
Grade 2	11 (15.5%)
Grade 3	50 (70.4%)

Table 2: Relationship between Ca-125 and stage.

Stage	N	Mean Ca -125	SD	SE	%95 CI	P
Stage 1	13 (18.3%)	331	224	62	195-467	< 0.001
Stage 2	15 (21.1%)	724	459	118	470-979	
Stage 3	23 (32.4%)	1186	985	205	760-1612	
Stage 4	20 (28.2%)	2134	1092	244	1623-2645	

The mean Ca-125 levels of the study patients were 331, 724, 1186 and 2134 in stage I, stage II, stage III and stage IV, respectively. A comparison of Ca-125 levels between stages revealed Ca-125 levels to be significantly increased with the increasing stage ($p < 0.001$) (Table 2).

(One-way ANOVA/ Standard deviation (SD), Standard Error (SE) Confidence interval (CI)

When the patients were grouped according to the degree of differentiation, 14.1% were grade I, 15.5% grade II and 70.4% were grade III. When the Ca-125 level and degree of differentiation were used to compare patients, no significant difference was identified between grades I and II ($p > 0.05$), while the difference was significant with increasing grade ($p < 0.001$), with the difference between grades II and III being significant (Table 3).

(One-way ANOVA/ Standard deviation (SD), Standard Error (SE) Confidence interval (CI)

The mean NLR was 2.69, 4.79 and 6.7 at grades I, II and III, respectively. While the difference between grades I and II was not significant, there was a significant difference between grades I and III (Table 4).

(One-way ANOVA/ Standard deviation (SD), Standard Error (SE) Confidence interval (CI)

When the patients were evaluated in terms of NLR, the mean NLR was 3.28, 6.53, 6.73 and 6.76 at stages I, II, III and IV, respectively. A significant difference was identified between NLR and stage ($p < 0.05$) (Table 5).

(One-way ANOVA / Standard deviation (SD), Standard Error (SE) Confidence interval (CI).

Discussion

The aim of this study was to evaluate the relationship between stage and grade of ovarian serous cancers with Ca 125 and NLR as an inflammatory parameter. There are very few publications in the literature that determine the relationship between NLR and Ca 125 with grade and stage. Ca-125 is a frequently used parameter for the prediction of advanced-stage disease, optimal debulking and platinum resistance in epithelial ovarian cancers, and especially for serous carcinomas. Ca-125 levels are relatively low in early-stage serous ovarian cancers, and increase with the increased tumor expansion and burden. Ca-125 levels have been shown to increase proportionally with increased stage and tumor burden, and are known to elevate in some other organ pathologies (tubal pathologies, endometriosis, liver cirrhosis, inflammatory pelvic diseases, pregnancy, etc.). Therefore, its specificity in ovarian cancers is debatable. Besides, the sensitivity and specificity of Ca-125 in the differentiation of benign and malignant tumors of the ovary are low [9,10]. Furthermore, the use of a single reference value or range of Ca-125 may not be appropriate for the prediction of prognosis of all serous ovarian tumors. The inconsistent findings of different studies may also be attributed to the nonspecific use of Ca-125 in all types of EOC. Therefore, the present study examined the association of Ca-125 and NLR with the degree of differentiation and tumor stage, rather than the differentiation of benign and malignant tumors in serous ovarian cancers. We established increased Ca-125 levels with increased tumor burden, stage, and degree of differentiation, and the levels decreased significantly when the tumor burden was decreased by tumor resection. Zivanovic et al. combined the decline in serum Ca-125 levels with the results of debulking surgery, and reported that optimally debulked patients in the “steep decline” group ($\geq 80\%$ reduction in Ca-125 levels) were at a lower risk of recurrence than patients with a lower Ca-125 decline [11].

A 2010 study by Kang S. et al. showed that the higher the Ca-125 level, the lower the optimal cytoreduction rate, and a pretreatment Ca-125 level ≥ 500 U/ml had a significantly poorer prognostic effect on mean survival, overall survival and progression-free survival when compared to Ca-125 < 500 U/ml in optimally cytoreduced patients. The authors reported that an evaluation of clinical and radiological parameters may contribute to the determination of the optimal treatment strategy, and suggested that since there is currently no single noninvasive parameter to predict optimal cytoreduction, such patients may be selected based on pretreatment Ca-125 levels [12]. In

Table 3: Relationship between Ca-125 and grade.

Grade	N	Mean Ca-125	SD	SE	%95 CI	P
Grade 1	10 (14.1%)	295	214	67	141-448	<0.001
Grade 2	11 (15.5%)	443	187	56	318-569	
Grade 3	50 (70.4%)	1546	1078	152	1239-1852	
Total	71 (100%)	1199	1057	125	948-1449	

Table 4: Relationship between grade and NLR.

Grade	N	MeanNLR	SD	SE	%95 CI	P
Grade 1	10 (14.1%)	2.69	0.51	0.16	2.32-3.06	< 0.001
Grade 2	11 (15.5%)	4.79	1.08	0.32	4.06-5.5	
Grade 3	50 (70.4%)	6.70	2.78	0.39	5.9-7.49	
Total	71 (100%)	5.80	2.78	0.33	5.1-6.5	

Table 5: Relationship between stage and NLR.

Stage	N	Mean NLR	SD	SE	%95 CI	P
Stage 1	13 (18.3%)	3.28	0.99	0.27	2.68-3.8	0.002
Stage 2	15 (21.1%)	6.53	2.87	0.74	4.93-8.1	
Stage 3	23 (32.4%)	6.73	2.74	0.57	4.8-7.2	
Stage 4	20 (28.2%)	6.76	2.71	0.60	5.49-8	

the present study, the increase in Ca-125 levels was not so significant between stage 1 and 2, while Ca-125 levels were significantly increased in patients at more advanced stages than stage II, which was attributed to the increased tumor burden. Another aim of our study was to evaluate the association between Ca-125 levels and the degree of tumor differentiation. Similarly, the higher the degree of differentiation, the higher the Ca-125 levels. Ca-125 levels were not significantly increased at grade 1, while there were significant increases in grade 2 and grade 3. The rate of positive lymph nodes was higher in patients with a high Ca-125 level, advanced-stage disease and advanced-grade tumors. This suggested that the rate of optimal cytoreduction may be lower and prognosis may be poorer in such patients.

There are few studies in the literature evaluating the relationship between stage and grade with NLR in serous ovarian cancer. Inflammation is a significant component of tumor progression. The tumor micro environment, regulated by inflammatory cells, plays a substantial role in the stimulation of proliferation and migration in neoplastic conditions [13,14]. Although the actual mechanism is still unclear, there have been several studies to date investigating the link between chronic inflammation and cancer [15]. Recent studies have suggested the use of the peripheral blood NLR as a prognostic marker for malignant tumors. Systemic inflammatory response includes secondary changes in the circulating leukocyte count [16]. Tumors inhibit the apoptosis of leukocyte-mediated inflammatory cytokines and promote angiogenesis, leading to tumor growth, progression and metastasis. Markers such as neutrophilia, lymphocytopenia, NLR and platelet-to-lymphocyte ratio (PLR) have been recently suggested to be associated with advanced-stage disease and to have prognostic significance [17]. In the present study, we evaluated the association between NLR and two significant prognostic factors; tumor stage and grade. Previous studies have also revealed these inflammatory markers to be significant in survival, together with Ca-125 levels, in postoperative residual disease and epithelial ovarian cancers [17,18]. Specific leukocyte differential counts (neutrophils, monocytes and platelets) and systemic inflammatory response markers (NLR and PLR) increase with increasing inflammatory burden, such as in cancer [19], whereas Ca-125 levels are relatively low in early-stage ovarian cancers because the levels of Ca-125 generally increase in advanced stages due to increased tumor burden. One of the objectives of the present study was to evaluate the degree of change in NLR in early-stage serous ovarian cancer. Consistent with the literature, we established that increased specific leukocyte differential counts and systemic inflammatory response markers such as NLR, in addition to high Ca-125 levels, can better predict advanced-stage disease or suboptimal shrinkage [20].

Previous studies have demonstrated that high neutrophil counts and low lymphocyte counts are associated with poor prognosis in EOC [21]. In the present study, the mean NLR was 5.8 in overall patients, but increased with increasing stage, and the difference

in NLR between the stages was significant. We also found that NLR did not significantly differ between patients with grade I and II tumors, while there was a significant difference between those with grade I and grade III tumors. As well, the Ca-125 level did not significantly differ between stage I and stage II patients, while there was a significant difference in NLR between stage I and stage II patients. This finding indicated that NLR was increased even in the early stages. The mechanism underlying the prognostic value of NLR, as a significant inflammatory marker, may be linked to the association between high NLR and inflammation. In neutrophilia, associated host cells, such as tumor cells and leukocytes, produce inflammatory cytokines and chemokines, and there have been studies reporting that this condition may contribute to the further progression of malignant tumors by releasing tumor growth factors such as vascular endothelial growth factor [17]. That said, it is obvious that neutrophilia, as an inflammatory response to cancer, inhibits the immune system by suppressing the cytotoxic activity of immune cells such as lymphocytes and natural killer cells [22]. NLR reflects these inflammatory changes, and thus may be considered a beneficial marker in patients with cancer for which more reliable biomarkers are unavailable [23].

A recent meta-analysis presented the results of studies similarly suggesting NLR to be associated with a high risk of mortality in solid tumors, since neutrophils may stimulate various cytokines with a wider spectrum of properties compared to platelets [24]. Neutrophils are cells that are at the center of inflammatory response. Previous studies on the prognostic significance of absolute neutrophil count have suggested that blood neutrophil count provides important information on the monitoring of cancer progression, the prediction of possible complications, and the assessment of patient response to treatment [25].

Conclusion

In conclusion, the combined use of pretreatment inflammatory parameters in serous ovarian cancers may provide information on the prognosis of the disease. In line with the literature, our study established increased NLR with increasing tumor stage and grade, which are important factors in tumor prognosis. In a further agreement with the literature, the present study provides evidence of the potential independent prognostic value of the lowest Ca-125 level in serous ovarian cancers.

The main limitations of the present study were the small sample size; the short duration of follow-up due to several social factors; and the non homogeneous patient population, since the majority of patients presenting to our hospital had early-stage disease. The findings of the present study should be supported by future studies with a longer follow-up and a larger number of cases.

As a result, in malignant serous ovarian tumors, Ca 125 and NLR increase in correlation with the grade and stage of the tumor. Our results are consistent with the literature

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