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Prognostic significance of pretreatment clinical and laboratory features in patients with ovarian cancer receiving neoadjuvant chemotherapy

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ABSTRACT

Introduction. In this study, we aimed to investigate the effects of pre-treatment clinical and laboratory characteristics on prognosis in ovarian cancer patients diagnosed in our clinic. In all patients, surgery was not possible, and they were qualified for neoadjuvant treatment.

Material and methods. Records of 96 patients diagnosed with ovarian carcinoma, who were not eligible for the surgery at the time of diagnosis and who were qualified for neoadjuvant treatment, were reviewed retrospectively.

Results. For the prognosis of OS, we analyzed age ($p = 0.106$), ECOG ($p = 0.007$), menstrual status ($p = 0.211$), FIGO stage ($p = 0.314$), ovarian origin of cancer ($p = 0.571$), albumin ($p = 0.496$), LDH ($p = 0.940$), CA-125 ($p = 0.032$), neutrophil-lymphocyte ratio (NLR) ($p = 0.194$), platelet-lymphocyte ratio (PLR) ($p = 0.002$), systemic immune-inflammation index (SII) ($p = 0.028$), prognostic nutritional index (PNI) ($p = 0.042$), Charlson Comorbidity Index (ACCI) ($p = 0.008$), Cumulative Illness Rating Scale (CIRS) ($p = 0.769$), chemotherapy response score (CRS) ($p = 0.235$), cytoreduction ($p = 0.006$), the number of cycles of neoadjuvant chemotherapy (NACT) ($p = 0.749$), and the total number of cycles of both neoadjuvant and adjuvant treatment ($p = 0.014$).

For the prognosis of DFS, we analyzed age ($p = 0.697$), ECOG ($p = 0.088$), menstrual status ($p = 0.912$), FIGO stage ($p = 0.728$), ovarian origin of cancer ($p = 0.463$), albumin (0.688), LDH ($p = 0.028$), CA-125 ($p = 0.160$), NLR ($p = 0.417$), PLR ($p = 0.442$), SII ($p = 0.069$), PNI ($p = 0.779$), ACCI ($p = 0.487$), CIRS ($p = 0.858$), CRS ($p = 0.235$) cytoreduction ($p < 0.001$), the number of cycles of NACT ($p = 0.849$), and the total number of cycles of both neoadjuvant and adjuvant treatment ($p = 0.188$).

Conclusions. ECOG status, pre-treatment CA-125 level, pre-treatment immune-based markers PLR, SII, and PNI, among comorbidity scores: the ACCI score, total number of cycles of neoadjuvant and adjuvant treatment, and cytoreduction type were found to be factors affecting OS. Serum LDH level and cytoreduction type were the factors affecting DFS.

Keywords: neoadjuvant treatment, ovarian cancer, survival, immune-based markers, comorbidity indexes

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Introduction

Ovarian cancer is the 8th most common cause of cancer-related mortality in women and the most common cause of gynecological cancer-related mortality in developed countries [1]. Approximately 75% of patients are in the advanced stage at diagnosis [International Federation of Gynecology and Obstetrics (FIGO) stage IIIC–IV] with a 5-year survival rate of less than 30% despite advances in cancer treatment [2]. While epithelial

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ovarian cancers are responsible for approximately 90% of ovarian cancers, high-grade serous ovarian carcinomas are the most common subtype in this group [3].

Until recently, the preferred approach has been primary debulking surgery followed by adjuvant platinum-based chemotherapy (CT). However, neoadjuvant chemotherapy followed by interval debulking surgery has recently become increasingly popular as an alternative treatment modality [4, 5]. Despite treatment, recurrence develops in most patients, and the desired survival level cannot be achieved [6]. For this reason, markers to predict treatment success have been investigated.

Previous studies have shown that optimal cytoreductive surgery, comorbidity indexes such as the Charlson Comorbidity Index, chemotherapy response score (CRS), immune indexes such as the neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and laboratory values such as serum CA-125 level affect prognosis and survival in ovarian cancer patients [7–10].

In this study, we aimed to investigate the effects of pre-treatment clinical and laboratory characteristics on prognosis in ovarian cancer patients diagnosed in our clinic, not eligible for surgery at the time of diagnosis, and qualified for neoadjuvant treatment.

Material and methods

We retrospectively investigated patients admitted to our medical oncology clinic between June 2019 and January 2023. They had a histopathological diagnosis of ovarian cancer and were not eligible for surgery at the time of diagnosis so they were qualified for neoadjuvant treatment. Ninety-six patients over the age of 18 years who met the inclusion criteria were included in our study. Clinicopathologic features, laboratory values, and treatment information were obtained from the hospital archive. Staging of the patients was performed according to the FIGO 2009 staging system. Laboratory values and clinical characteristics of the patients before the start of treatment were recorded.

Disease-free survival (DFS) was defined as the time from the first neoadjuvant chemotherapy to the time of relapse. Overall survival (OS) was evaluated as the time from the date of pathologically confirmed diagnosis until death for any reason.

The NLR was calculated as the number of neutrophils divided by the number of lymphocytes, and the PLR was calculated as the number of platelets divided by the number of lymphocytes. The systemic immune-inflammation index (SII) was obtained by multiplying the platelet count by the NLR. The prognostic nutritional index (PNI) was obtained by adding 0.005 × lymphocyte value (in mm^3) to albumin value (mg/dL). Comorbidity indexes for all patients were calculated by the age-adjusted Charlson Comorbidity Index (ACCI) and the Cumulative Illness Rating Scale (CIRS) (Tab. 1).

The laboratory limits were used to find cut-off points to group patients according to such variables as age, laboratory values, immune indices, and comorbidity indices. Receiver operating characteristic (ROC) analysis was used for variables without laboratory limits. Pearson chi-squared and Fisher's exact tests were used to examine differences between these two groups. OS and DFS times were calculated by the Kaplan-Meier method. The log-rank test was used to compare the results. The Cox regression model was used to analyze independent prognostic risk factors. p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences software program version 25.0 (SPSS Inc., Chicago, IL, US).

Due to the retrospective study design, informed consent was not collected from patients. Our Hospital Clinical Research Ethics Committee decided that informed consent was not required and ethical approval was obtained for the multicentric study (Date: 18.8.2023/No: 3899).

Results

Between June 2019 and January 2023, 96 patients with a median age of 60.52 years (range 35.38 to 85.66) were included. Most patients had Eastern Cooperative Oncology Group (ECOG) performance scores of 1 (n = 43, 44.8%) and 2 (n = 31, 32.3%). According to the FIGO staging system, 53 (55.2%) patients were in stage IIIc, while 43 (44.8%) were in stage IV. Thirteen (13.5%) of the patients were premenopausal, and 82 (85.4%) were postmenopausal. The patients' clinical, laboratory, and treatment modalities are presented in Table 2.

When OS was analyzed according to the clinical characteristics of the patients, age (p = 0.106), ECOG (p = 0.007), menstrual status (p = 0.211), smoking (p = 0.312), FIGO stage (p = 0.314), and ovarian origin of cancer (p = 0.571) were analyzed. According to this analysis, patients with ECOG 0–1 had median OS of 47.34 months (confidence interval was not reached using Kaplan-Meier analysis), while patients with ECOG: 2–3 had median OS of 21.82 months [95% confidence interval (CI) 12.42–31.211], with a statistically significant difference between these two groups. When DFS was analyzed according to the clinical characteristics of the patients, age (p = 0.697), ECOG (p = 0.088), menstrual status (p = 0.912), smoking (p = 0.544), FIGO stage (p = 0.728), and ovarian origin of cancer (p = 0.463) were analyzed. According to this analysis,

Table 1. Charlson Comorbidity Index and Cumulative Illness Rating Scale

Charison Scale		Cumulative Illness Rating Scale	
Comorbidity	**Points**	**System**	**Score**
Myocardial infarction	1	Heart	0–4
Congestive heart failure	1	Vascular	0–4
Peripheral vascular disease	1	Hematopoietic	0–4
Cerebrovascular disease	1	Respiratory	0–4
Dementia	1	Eyes, ears, nose, throat	0–4
Chronic pulmonary disease	1	Upper gastrointestinal system	0–4
Connective tissue disease	1	Lower gastrointestinal system	0–4
Ulcer disease	1	Liver	0–4
Mild liver disease	1	Renal	0–4
Diabetes (without complications)	1	Genitourinary	0–4
Diabetes with end-organ damage	2	Musculoskeletat/integument	0–4
Hemiplegia	2	Neurologic	
Moderate or severe renal disease	2	Endocrine/metabolic and breast	0–4
Second solid tumor (non-metastatic)	2		
Leukemia	2		
Lymphoma, multiple myeloma	2	Psychiatric illness	0–4
Moderate or severe liver disease	3		
Second metastatic solid tumor	6		
Acquired immunodeficiency syndrome	6		

Rating strategy: 0 — no problem; 1 — current mild problem or past significant problem; 2 — moderate disability or morbidity/requires "first line" therapy; 3 — severe/constant significant disability/"uncontrollable" chronic problems; 4 — extremely severe/immediate treatment required/end-organ failure/severe impairment in function

no statistically significant variable for DFS was observed among these clinical characteristics. A summary of the survival analysis is presented in Table 3.

The OS values were analyzed according to the laboratory data collected from patients on the first admission, and the inflammation-based markers obtained from these values. According to this analysis, albumin ($p = 0.496$), lactate dehydrogenase (LDH) ($p = 0.940$), C-reactive protein (CRP) ($p = 0.371$), CA-125 ($p = 0.032$), and inflammation-based markers: NLR ($p = 0.194$), PLR ($p = 0.002$), SII ($p = 0.028$), and PNI ($p = 0.042$) values were divided into two groups according to cut-off values. When the groups with statistically significant differences were analyzed in detail, the median OS rate was 47.34 months (confidence interval was not reached using Kaplan-Meier analysis) in the CA-125 ≤ 839.55 group and 29.77 months (95% CI 16.21–43.33) in the CA > 839.55 group. The median OS rate was 47.34 months (confidence interval was not reached using Kaplan-Meier analysis) in the group with a PLR ≤ 255.21 and 21.13 months (95% CI 8.84–33.41) in the group with a PLR > 255.21. With regard to the SII, the median OS rate was 47.34 months (CI was not reached using Kaplan-Meier analysis) in the group with an SII ≤ 1527.6, while the median OS rate was 36.01 months (95% CI 18.19–53.82) in the group with an SII > 1527.6. In the group with a PNI ≤ 45.9, the median OS rate was 20.21 months (CI was not reached using Kaplan-Meier analysis). In contrast, median OS in the group with a PNI > 45.9 was 47.34 months (CI with Kaplan-Meier analysis was not run).

Disease-free survival values were analyzed according to the laboratory data collected on the initial presentation, and inflammation-based markers were derived from these values. According to this analysis, albumin (0.688), LDH ($p = 0.028$), CRP ($p = 0.055$), CA-125 ($p = 0.160$), and inflammation-based markers: NLR ($p = 0.417$), PLR ($p = 0.442$), SII ($p = 0.069$), and PNI ($p = 0.779$) values were divided into two groups according to cut-off values. When the groups with statistically significant differences were analyzed in detail, median DFS was 15.61 months (95% CI 9.40–21.81) in the LDH ≤ 246 group, while median DFS was 13.01 months (95% CI 11.28–14.74) in the LDH > 246 group.

Charlson Comorbidity Index ($p = 0.008$) and CIRS scores ($p = 0.769$) were analyzed when OS values were analyzed according to comorbidity indices. According to

Table 2. Clinical, laboratory, and treatment characteristics of patients

Variant	No. of patients (%)
Age [years]	
Median	60.52
Range	35.38–85.66
ECOG	
0	10 (10.4)
1	43 (44.8)
2	31 (32.3)
3	9 (9.4)
FIGO stage	
IIIC	53 (55.2)
IV	43 (44.8)
Menstrual status	
Premenopausal	13 (13.5)
Postmenopausal	82 (85.4)
Smoking	
Yes	80 (83.3)
No	16 (16.7)
Ovary with cancer	
Left	13 (13.5)
Right	19 (19.8)
Bilateral	59 (61.5)
Pre-treatment CA-125	
≤ 839.55	43 (44.8)
> 839.55	50 (52.1)
Pre-treatment LDH	
≤ 246	36 (37.5)
> 246	56 (58.3)
Cytoreduction	
Maximal	68 (70.8)
Non-maximal	13 (13.5)
Number of cycles of neoadjuvant CT	
≤ 3	63 (65.6)
> 3	33 (34.4)
Total number of cycles of neoadjuvant and adjuvant CT	
≤ 6	65 (67.7)
> 6	27 (28.1)

CT — chemotherapy; ECOG — Eastern Cooperative Oncology Group; FIGO — International Federation of Gynecology and Obstetrics; LDH — lactate dehydrogenase

this analysis, median OS in the group with ACCI ≤ 7.5 was 47.34 months (confidence interval was not reached using Kaplan-Meier analysis). In comparison, median OS in the group with an ACCI > 7.5 was 21.13 months (95% CI 18.6–23.65). When the DFS values were analyzed according to the comorbidity indices, no statistically significant difference was observed between the ACCI ($p = 0.487$) and CIRS ($p = 0.858$) groups in determining DFS.

When the pathology results were analyzed, for OS, KI-67 ($p = 0.232$) and CRS ($p = 0.235$) were observed, and for DFS, KI-67 ($p = 0.232$) and CRS ($p = 0.235$) were observed. We thought that the factors mentioned in the pathology did not prognostically affect OS and DFS.

When OS was analyzed according to treatment modalities, cytoreduction ($p = 0.006$), number of cycles of neoadjuvant CT ($p = 0.749$), and total number of cycles of both neoadjuvant and adjuvant treatments ($p = 0.014$) were analyzed. Median OS in the maximal cytoreduction group could not be reached using Kaplan-Meier analysis; median OS in the non-maximal cytoreduction group was 21.82 months (95% CI 13.36–30.28), and there was a statistically significant difference between the two groups. While median OS in the group with a total cycle number ≤ 6 was not reached using Kaplan-Meier analysis, median OS in the group with a total cycle number > 6 was 47.34 months (confidence interval was not reached using Kaplan-Meier analysis), and a statistically significant difference was observed between the groups. When DFS was analyzed according to treatment modalities, cytoreduction ($p < 0.001$), number of cycles of neoadjuvant CT ($p = 0.849$), and total number of cycles of both neoadjuvant and adjuvant treatments ($p = 0.188$) were analyzed. The median DFS rate in the maximal cytoreduction group was 16.03 months (95% CI 11.54–20.53), while the median DFS rate in the non-maximal cytoreduction group was 10.78 months (95% CI 6.32–15.23), with a statistically significant difference between the two groups.

Discussion

Our study examined the factors affecting prognosis in ovarian cancer patients who were not eligible for surgery at the time of diagnosis and who were qualified for neoadjuvant treatment. Although most of these variables have been discussed in ovarian cancer in general, studies examining the factors affecting prognosis in neoadjuvant treatment in detail are very few. In our study, ECOG status, pre-treatment CA-125 level, pre-treatment immune-based markers: the PLR, SII, and PNI, among comorbidity scores: ACCI score, total number of cycles of neoadjuvant and adjuvant treatment, and cytoreduction type were found to be factors affecting OS. Serum LDH level and cytoreduction type were the factors affecting DFS.

In the study by Yoshikawa et al. [11], age was not found to be a factor affecting prognosis in ovarian cancer patients. At the same time, it was emphasized that

Table 3. Prognostic factors for overall survival (OS) and disease-free survival (DFS)

Variables		p-value for OS	p-value* for DFS
Age [years]	≤ 56.7 *vs.* > 56.7	0.106	0.697
ECOG	0–1 *vs.* 2–3	**0.007**	0.088
Menstrual status	Pre *vs.* post-menopausal	0.211	0.912
Smoking	Yes *vs.* no	0.312	0.544
FIGO stage	IIIC *vs.* IV	0.314	0.718
Origin of cancer	Unilateral *vs.* bilateral	0.571	0.463
Ca-125	≤ 839.55 *vs.* > 839.55	**0.032**	0.600
Albumin	≤ 32 *vs.* > 32	0.496	0.688
LDH	≤ 246 *vs.* > 246	0.940	**0.028**
CRP	≤ 48.25 *vs.* > 48.25	0.371	0.055
NLR	≤ 3.72 *vs.* > 3.72	0.424	0.314
PLR	≤ 255.21 *vs.* > 255.21	**0.002**	0.318
SII	≤ 1527.6 *vs.* > 1527.26	**0.018**	0.069
PNI	≤ 45.9 *vs.* > 45.9	**0.042**	0.779
ACCI	≤ 7.5 *vs.* > 7.5	**0.008**	0.487
CIRS	≤ 7.5 *vs.* > 7.5	0.769	0.858
Ki-67	≤ 35 *vs.* > 35	0.232	0.628
CRS	1–2 *vs.* 3	0.235	0.345
Number of NACT cycles	≤ 3 *vs.* > 3	0.749	0.849
Total number of cycles	≤ 6 *vs.* > 6	**0.014**	0.188
Cytoreduction	Maximal *vs.* non-maximal	**0.006**	**< 0.001**

*p < 0.05; ACCI — Age-adjusted Charlson Comorbidity Index; CIRS — Cumulative Illness Rating Scale; CRP — C-reactive protein; CRS — chemotherapy response score; ECOG — Eastern Cooperative Oncology Group; FIGO — International Federation of Gynecology and Obstetrics; LDH — lactate dehydrogenase; NACT — neoadjuvant chemotherapy; NLR — neutrophil-lymphocyte ratio; PLR — platelet-lymphocyte ratio; PNI — prognostic nutritional index; SII — systemic immune-inflammation index

there was a relationship between performance status and prognosis [11]. In the study by Deng et al. [12], the prognosis was worse in elderly patients. In the study by Cioffi et al. [13], no relationship was found between age and prognosis in ovarian cancer patients receiving neoadjuvant treatment. In the study by Carey et al. [14], performance status was observed as a factor affecting both OS and PFS in ovarian cancer patients. In our study, age did not affect either OS or PFS, and a significant relationship was found between ECOG status and OS, affecting prognosis.

A study by Chen et al. [15] showed that the CA-125 level measured before treatment affected OS prognosis in ovarian cancer patients. In our study, patients with high CA-125 levels had statistically significantly lower OS than those with low CA-125 levels. Ikeda et al. [16] showed that platinum resistance was higher and DFS was shorter in patients with higher LDH levels. In our study, although no correlation was observed between LDH levels and OS, it was observed that patients with higher LDH levels had shorter DFS.

Liontos et al. [17] showed that CRS did not prognostically affect OS but affected PFS. Böhm et al. [18] demonstrated that patients with a CRS score of 3 had better OS and PFS. Our study observed no prognostic relationship between CRS and OS or DFS.

In many previous studies, immune-based markers such as the NLR, PLR, SII, and PNI have been observed to affect prognosis in lung, pancreatic, colon, and many other cancer types [19–21]. When we look at the role of these indexes in ovarian cancer, both the study by Kim et al. [22] and Huang et al. [9] showed that the NLR level affects OS in ovarian cancer patients. In our research, it was observed that NLR did not affect either OS or DFS prognosis. Zhu et al. [23] found that the PLR value affected both OS and DFS in ovarian cancer patients. In our study, while the PLR was a prognostic factor for OS, it did not affect DFS. Ceran et al. [24] also observed that PLR affected OS. Mao et al. [25] showed that patients with a high SII had a worse prognosis. In our study, the SII was also a factor affecting poor prognosis. When the relationship between the PNI and prognosis

in ovarian cancer patients was analyzed, we observed that patients with low PNI scores had a worse prognosis in both the study by Dai et al. [26] and Komura et al. [27]. In our study, the OS rate of patients with low PNI values was statistically significantly lower.

It has been previously shown that there is a relationship between comorbidity indexes and prognosis in many cancer types, such as lung cancer, glioblastoma multiforme, and soft tissue sarcoma [28, 29]. In studies examining the relationship between prognosis and comorbidity indices in ovarian cancer, Kahl et al. [30] showed that OS was lower in patients with higher ACCI scores. Similarly, in the study by Tetsche et al. [31], OS was observed to be shorter in the group with higher ACCI scores and comorbidity. In our study, we noted that patients with high ACCI scores had shorter OS than patients with low ACCI scores.

Regarding treatment of ovarian carcinoma patients qualified for neoadjuvant treatment, there is still no consensus on many issues, such as the timing of the cycles, total number of cycles, and optimum time of surgery. Both Prader et al. [32] and Bristow et al. [33] reported that maximal cytoreduction is the most critical factor determining OS. In our study, we observed that maximal cytoreduction significantly increased both OS and DFS. Xu et al. [34] showed that the PFS and OS rates of patients had a worse prognosis when the number of cycles given in neoadjuvant treatment increased. Minareci et al. [35] showed that when the number of cycles given in neoadjuvant treatment increased, DFS was not affected, but OS decreased. In the study by Akladios et al. [36], no significant relationship was found between the number of cycles given in neoadjuvant treatment and OS. Our study found no relationship between the number of cycles given in neoadjuvant treatment and prognosis. Chung et al. [37] demonstrated that exceeding 6 doses in neoadjuvant and adjuvant treatment did not affect survival. Our study showed that OS increased as the total number of cycles of both neoadjuvant and adjuvant treatment increased, whereas DFS was unaffected.

Our study has some limitations. It was a retrospective study, and not all information could be accessed due to the file system. Even though we analyzed nearly 100 patients, it was not a very large population. In the future, more comprehensive and prospective studies should be conducted to determine more accurately the factors affecting prognosis in ovarian cancer patients who are qualified for neoadjuvant treatment.

Conclusions

In our study, ECOG status, pre-treatment CA-125 level, pre-treatment immune-based markers PLR, SII, and PNI, among comorbidity scores: the ACCI score, the total number of cycles of neoadjuvant and adjuvant treatment, and cytoreduction type were found to be factors affecting OS in ovarian cancer patients receiving chemotherapy. Serum LDH level and cytoreduction type were the factors affecting DFS.

Article Information and Declarations

Data availability statement

The patients' data were included in the study with ethics committee approval. It is not suitable for sharing.

Ethics statement

Ethics committee approval was received.

Author contributions

S.S.: contributions to the conception, revising, and final approval of the version to be published, agree to be accountable for all aspects of the work; D.B., S.C.F., G.U., M.A.N.S., F.T.K.: contributions to the drafting of the work, final approval of the version to be published, agree to be accountable for all aspects of the work.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary material

None.

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