ORIGINAL RESEARCH

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Expression of Her2/Neu, MUC1, Estrogen, and Progesterone Receptors in Epithelial Ovarian Cancer: Implications for Targeted Therapy: A Descriptive Research

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ABSTRACT Objective: This study aimed to investigate the expression of HER2neu, MUC1, and estrogen and progesterone receptors in malignant epithelial ovarian cancer (EOC) and determine their effects on clinical-pathological features and prognosis. **Material and Methods:** The study included 86 patients diagnosed with EOC. The histopathological types were high-grade serous carcinoma (HGSC; n=46 patients), low-grade serous carcinoma (LGSC; n=7 patients), mucinous carcinoma (MC; n=14 patients), and clear cell carcinoma (CCC; n=19 patients). The patients'' demographic, clinical-pathological, and prognostic characteristics were reviewed retrospectively. The pathological separates of the patients were immunohistochemically applied with MUC1, HER2neu, estrogen, and progesterone antibodies, and the expression status of these markers was analyzed for their relationship with clinical-pathological features and prognosis using statistical methods. **Results:** MUC1 was strongly positive in LGSC and CCC patients, with a lower frequency in MC and higher in HGSC ($p<0.001$). In 50% of MC cases, HER2neu staining was strongly positive. In addition, 85.7% of LGSC cases had positive estrogen receptor (ER) ($p=0.041$) and progesterone receptor (PR) ($p=0.029$). All 16 patients in the HGSC group, who were resistant to platinum therapy, tested positive for ER staining. Additionally, 93.7% of these patients were highly positive for MUC1 staining. Independent prognostic factors include: lymph node metastasis odds ratio [(OR)=3.5], lymphovascular invasion (LVI) (OR=21.296), advanced stage (OR=13.442), platinum resistance (OR=46.588), grade 3 (OR=10.750), ER positivity (OR=3.438), optimal cytoreduction (OR=17.280), and HGSC (OR=9.257). **Conclusion:** The study found that MUC1 was highly positively stained in the LGSC and CCC groups, platinum-resistant patients had high estrogen-PR expressions, and half of the MC group tested positive for HER2neu. These results are important for targeted therapy in difficult-to-manage EOC.

Keywords: Clear cell carcinoma; epithelial ovarian cancer; HER2neu; high grade serous ovarian cancer; low grade serous ovarian cancer; MUC1; mucinous cancer; estrogen receptor; progesterone receptor

Epithelial ovarian cancer (EOC) is the most common type of ovarian cancer, but we still have a limited understanding of its molecular and biological mechanisms. Although their histopathological and biological features are different, EOCs are grouped under the same heading and their management algorithms are very similar.[1] However, there is a need for more effective targeted therapies for certain types of EOCs, such as platinum-resistant serous tumors, low-grade serous ovarian carcinoma (LGSOC), mucinous carcinoma (MC), and clear cell carcinomas (CCC), as conventional chemotherapy has limited efficacy against them.

Mucins are glycoproteins, especially MUC1, which regulate cellular processes such as proliferation, apoptosis, adhesion, and invasion. Recent studies have demonstrated that mucins play a crucial role

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in the pathogenesis of many cancers, including colorectal, breast, pancreatic, ovarian, and gastric cancers. Abnormal mucin expression has been observed in these cancers, with cancer-associated MUC1 showing a different structure from normal MUC1.[2,3] In particular, malignant ovarian epithelial tumors have stronger mucin expression than benign and borderline tumors.[4] The HER2neu receptor, a member of the epidermal growth factor receptor family, which regulates cell growth, differentiation, and angiogenesis, is an oncogene found in 25-30% of breast and ovarian cancers. HER2/neu gene overexpression is a poor prognostic indicator in ovarian cancers.[5]

The estrogen receptor (ER) is a nuclear hormone receptor with 2 types: ER-alpha (ER-α) and ER-beta (ER-β). ER-β's role is not fully understood, but it differs significantly from ER-α in tissue distribution. ER-β is expressed in normal ovarian tissue, but it decreases during ovarian cancer development, causing epigenetic changes such as hypermethylation of promotor genes.[6] Estrogen seems to increase the movement and spreading of ovarian cancer cells with ER expression more common in serous and endometrioid carcinomas.[6,7] The progesterone receptor (PR) is an alpha- and beta-chain protein that promotes cell proliferation and is located in the nucleus and cytoplasm. While the impact of PR expression on ovarian cancer prognosis is not yet well-established, recent research suggests its positive effect on patient survival, making it an important receptor to consider in different cancer type.[8-10]

This study aimed to investigate how different EOC groups express MUC1, HER2neu, ER, and PR using immunohistochemical analysis (IHC). The study will also explore how the expression of these markers affects clinical-pathological features and prognosis.

MATERIAL AND METHODS

The study included 86 ovarian cancer patients who underwent surgery at the Çukurova University Faculty of Medicine's Department of Gynecology and Obstetrics between 2009-2018. Approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine with order number 42 on January 22, 2021 (numbered 107). Of these 86 patients, the pathological diagnosis was high-grade serous ovarian carcinoma (HGSOC) in 46, LGSOC in 7, MC in 14, and CCC in 19. We reviewed the clinical data of 477 ovarian cancer patients operated in our hospital during a specific period. Patients who had their first surgery elsewhere or did not follow-up with our hospital post-surgery were excluded from the study. The paraffin blocks of the patients to be included in the study were evaluated by 2 specialist pathologists, and those with primary ovarian tumors, especially MC, were included in the study. Metastatic patients and those with non-epithelial ovarian cancers were excluded from the study.

The retrospective review of the patients' data included age, menopause status, body mass index (BMI), fertility, tumor marker levels at admission, per-operative presence of ascites, LVI, lymph node metastasis status, stage and grades, total survival and disease-free survival (DFS) times, recurrence status, and platinum resistance. The patients underwent primary surgery including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic paraaortic lymph node dissection. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 staging system, and grading for mucinous tumors was also considered. HGSOC and CCC were classified as high grade, and LGSOC as low grade. The patients were divided into platinum-sensitive, platinum-semisensitive, and platinum-resistant groups based on the time of relapse.

The patients'' overall survival (OS) and DFS were calculated. OS was the time from the first diagnosis to death or last control, while DFS was the time from the first diagnosis to recurrence or last control.

PATHOLOGICAL PREPARATION AND IMMUNOHISTOCHEMICAL ANALYSIS

The tissue samples were taken from paraffin-embedded tissues after being treated with 10% formaldehyde. From these samples, 5-micron-thick sections were obtained and placed on slides to undergo hematoxylin-eosin (H&E) staining using an automated staining device (Leica ST 5020-Germany). The H&E

staining confirmed the histological subtypes of the pathological preparations, which included HGSC, LGSC, MC, and CCC. HER2neu, MUC1, ER, and PR antibodies were applied to the pathological samples of the studied patients using IHC. Tissues taken on pyolysin slides for immunohistochemical staining were exposed to ER (Leica, 6F-11, USA), PR (Leica, PGR-312-L-F, USA), cERB2 (GenomeMe, IHC042, Canada) and MUC1 (GenomeMe, IHC623, Canada) with a Ventana BenchMark XT model automated immunohistochemical staining device. Automated closure with a liquid-based covering material (Leica ST 5030-Germany) was applied to the separates stained in the automated staining device. H&E and immunohistochemical samples were evaluated under an Olympus BX46 light microscope at different magnifications by 2 expert pathologists.

In the immunohistochemical evaluation, the membranous staining of HER2/neu, the membranous and cytoplasmic staining of MUC1, and the nuclear staining of ER and PR in the tumor cells were evaluated as positive (Figure 1).

Membranous staining was considered for the HER2/neu antibody.

- 0: No staining
- +/+++ (1+): Cytoplasmic or weak incomplete staining
- ++/+++ (2+): Complete staining less strong than 10% or basolateral membranous staining
- +++/+++ (3+): Complete staining stronger than 10% or basolateral membranous staining
- In the statistical evaluation, 0 and 1+ staining was accepted as weak, and 2+ and 3+ staining was accepted as strong.[9]
- Cytoplasmic staining was considered for the MUC1 antibody.
- 0: No staining
- +/+++ (1+): Cases with staining less than 0-10%
- ++/+++ (2+): Cases with staining less than 10-60%
- +++/+++ (3+): Cases with staining of more than 60%

In the statistical evaluation, 0 and 1+ staining was accepted as weak, and 2+ and 3+ staining was

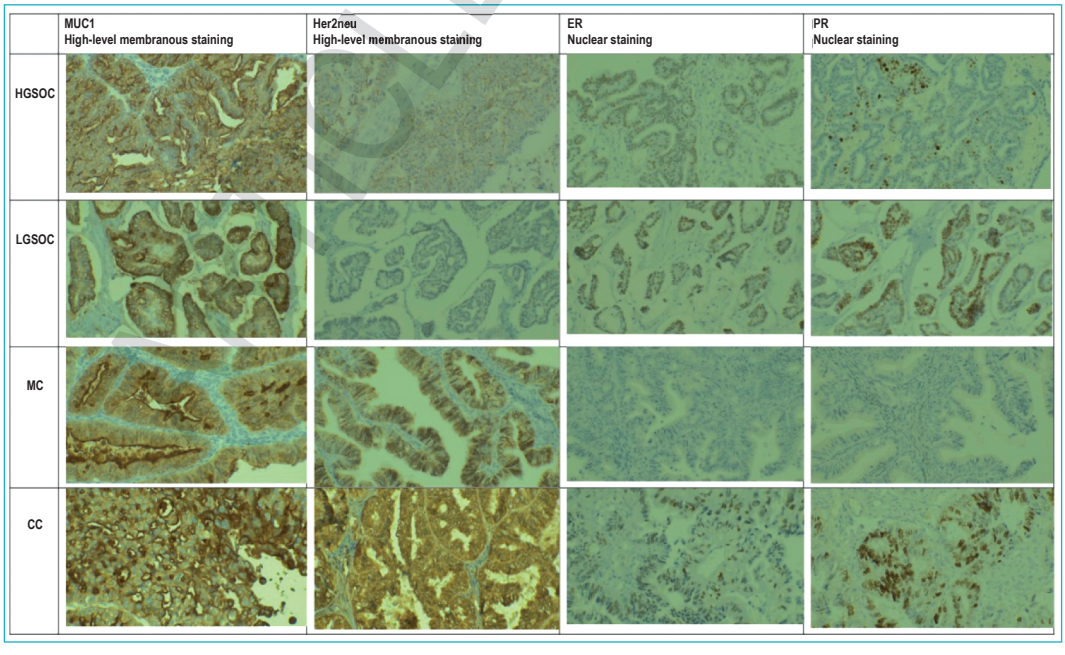

FIGURE 1: Membranous staining of HER2/neu, membranous and cytoplasmic staining of MUC1 and nuclear staining of ER and PR in tumor cells were evaluated as positive. ER: Estrogen receptor; PR: Progesterone receptor; HGSOC: High grade serous ovarian carcinoma; LGSOC: Low grade serous ovarian carcinoma; MC: Musinous ovarian carcinoma; CC: Clear cell ovarian carcinoma

accepted as strong.[10] In the immunohistochemical evaluation of ER and PR, nuclear staining in at least 1% of cells was considered positive.

STATISTICAL ANALYSIS

Categorical measurements are summarized as numbers and percentages, and continuous measurements are presented as mean and standard deviation (median and minimum-maximum where appropriate). The chi-square and Fisher exact tests were used to analyze categorical expressions. The Shapiro-Wilk test was employed to determine whether the parameters in the study showed a normal distribution. The independent Student's t-test was employed for normally distributed parameters, and the Mann-Whitney U test was employed for non-normally distributed parameters. The Kaplan-Meier and log-rank tests were used for survival analyses. Moreover, a multiple logistic regression model was used to determine the factors affecting mortality. Statistical significance level was considered as 0.05 in all tests. The SPSS 23.0 package program was used for the statistical analysis of the data.

RESULTS

In our study, the data of 86 patients, including 46 (53.5%) patients with HGSOC, 7 (8.1%) patients with LGSOC, 14 (16.3%) patients with MC, and 19 (22.1%) patients with CCC, were analyzed. The demographic, clinical-pathological, and prognostic characteristics of the 86 patients included in the study are given in Table 1. There was no significant difference between the histopathological types and mean age, BMI, and parity. Postmenopausal status was observed more frequently in HGSOC patients ($p=0.036$). The incidence of stage 3 disease was found to be higher in the HGSOC and LGSOC groups ($p<0.001$). The frequency of appendectomy was higher in patients with MC ($p=0.004$). The frequency of per-operative ascites over 500 ml was found to be higher in patients in the HGSOC group ($p<0.001$). When the amount of residual tumor after surgery was examined, the R0 resection grade was achieved in 57 (66.3%) patients after surgery. The R1 grade was achieved in 27 (31.4%) patients and the R2 grade in 2 (2.3%) patients. It was observed that resection at the R1 level was lower in patients in the CCC group ($p=0.007$). In the study, 66 (76.7%) patients underwent lymphadenectomy, with 29 (40.8%) of them having lymph node metastasis. There was no significant correlation found between histopathological types and lymph node metastasis. LVI was present in 54% of the patients, with a higher frequency in those with HGSOC. The presence of recurrence was detected in 45 (52.3%) patients. Of these patients, 36 (78.3%) had HGSOC, 1 (14.3%) had LGSOC, 3 (21.4%) had MC, and 5 (26.3%) had CCC pathology. The presence of recurrence was found to be more frequent in patients in the HGSOC group ($p<0.001$). The mortality rate was found to be higher in patients with HGSOC ($p<0.001$) (Table 1).

The receptor expressions of the research group were examined in Table 2 and it was found that MUC1 was highly stained in 77 (89.5%) patients. Of these patients, 44 (95.7%) had HGSOC, 7 (100%) had LGSOC, 7 (50%) had MC, and 19 (100%) had the histopathological type of CCC. High staining of MUC1 was remarkable in all patients with LGSOC and CCC histopathological types. Eleven (12.8%) patients were found to have high HER2neu staining. Among these patients, 1 (2.2%) had HGSOC, 7 (50%) had MC, and 3 (15.8%) had the histopathological type of CCC. It was remarkable that HER2neu was not highly stained at all in LGSOC histopathology and half of them were highly stained in MC. ER was positive in 53 (61.6%) patients. Of these patients, 41 (89.1%) had HGSOC, 6 (85.7%) had LGSOC, and 6 (31.6%) had the CCC type. While the highest ER positivity was observed in serous tumors, all cases were negative for ER in MC. PR positivity was detected in 33 (38.4%) patients. Of these patients, 24 (52.2%) had HGSOC, 6 (85.7%) had LGSOC, and 3 (15.8%) had the CCC type. It was notable that 6 (85.7%) of the LGSOC type patients were positive for PR. All patients in MC were found to be PR negative. PR was detected to be negative in 16 (84.2%) patients in the CCC group. While the highest staining rate in terms of PR was in the LGSOC group, PR was negative in MCs as for ER.

Table 3 presents the relationship between the MUC1, HER2Neu, EP, and PR expression levels and the clinical-pathological characteristics and progno-

TABLE 1: Examination of the clinical, pathological and prognostic features of the research group

	High grade serous n=46 X̄+SD	Low grade serous n=7 X̄+SD	Mucinous n=14 X̄+SD	Clear cell n=19 X̄+SD	p value
Age	55.7±9.8	51.4±16.2	48.4±13.9	52.4±11.6	0.195
BMI	30.3±5.0	31±6.9	30.6±3.9	28.7±4.3	0.576
	n (%)	n (%)	n (%)	n (%)	
Age					
Young between the ages of 18 and 45 years	8 (17.4)	4 (57.1)	6 (42.9)	7 (36.8)	0.064
Middle-aged between the ages of 45 and 59 years	22 (47.8)	2 (28.6)	6 (42.9)	5 (26.3)	
Elderly between the ages of 60 and 74 years	15 (32.6)	-	1 (7.1)	7 (36.8)	
Old between the ages of 75 and 89 years	1 (2.2)	1 (14.3)	1 (7.1)	-	
Menopause					
Premenopause	10 (21.7)	4 (57.1)	8 (57.1)	8 (42.1)	**0.036**
Postmenopause	36 (78.3)	3 (42.9)	6 (42.9)	11 (57.9)	
Parity					
Nulliparous	14 (30.4)	1 (14.3)	4 (28.6)	9 (47.4)	0.508
1 birth	6 (13)	-	1 (7.1)	1 (5.3)	
2 and more births	26 (56.4)	6 (85.7)	9 (64.3)	9 (47.4)	
BMI					
18.5-24.9 Normal	5 (10.9)	2 (28.6)	1 (7.1)	4 (21.1)	0.740
25-29.9 overweight	15 (32.6)	1 (14.3)	5 (35.7)	6 (31.6)	
>30 obese	26 (56.5)	4 (57.1)	8 (57.1)	9 (47.4)	
Status					
Alive	8 (17.4)	5 (71.4)	10 (71.4)	11 (57.9)	**<0.001**
Exitus	38 (82.6)	2 (28.6)	4 (28.6)	8 (42.1)	
Lymph node metastasis (+)	20 (54.1)	3 (50)	3 (23.1)	3 (20)	0.064
Stage					
Stage 1	2 (4.3)	-	9 (64.3)	12 (63.2)	**<0.001**
Stage 2	2 (4.3)	2 (28.6)	2 (14.3)	1 (5.3)	
Stage 3	42 (91.4)	5 (71.4)	3 (21.4)	6 (31.6)	
Stage group					
Early	4 (8.7)	2 (28.6)	11 (78.6)	13 (68.4)	**<0.001**
Late	42 (91.3)	5 (71.4)	3 (21.4)	6 (31.6)	
LVI (+)	40 (87)	4 (57.1)	3 (21.4)	8 (42.1)	**<0.001**
Surgical type					
TAH+BSO	-	-	-	5 (26.3)	**0.002**
TAH+BSO+OMENTECTOMY	9 (19.6)	-	2 (14.3)	4 (21.1)	
TAH+BSO+OMENTECTOMY+BPPLAND	37 (80.4)	7 (100)	11 (78.6)	10 (52.6)	
USO+BPPALND	-	-	1 (7.1)	-	
Additional surgery					
Colon resection	7 (50)	2 (100)	-	-	**0.004**
Upper abdominal surgery	3 (21.4)	-	-	-	
Appendectomy	4 (28.6)	-	9 (100)	-	
Peroperative ascites					
None	12 (26.1)	4 (57.1)	11 (78.6)	12 (63.2)	**<0.001**
Below 500 ml	8 (17.4)	3 (42.9)	2 (14.3)	5 (26.3)	
Above 500 ml	26 (56.5)	-	1 (7.1)	2 (10.5)	
Resection degree					
R0	23 (50)	4 (57.1)	14 (100)	16 (84.2)	**0.007**
R1	22 (47.8)	3 (42.9)	-	2 (10.5)	
R2	1 (2.2)	-	-	1 (5.3)	
Recurrence (+)	36 (78.3)	1 (14.3)	3 (21.4)	5 (26.3)	**<0.001**
Platinum resistance					
Sensitive	24 (52.2)	4 (57.1)	11 (78.6)	11 (57.9)	0.512
Semi-resistant	17 (37)	2 (28.6)	2 (14.3)	4 (21.1)	
Resistant	5 (10.9)	1 (14.3)	1 (7.1)	4 (21.1)	
OS (month)	41.4±4.2	99.8±22.8	80.4±1	75.9±13.7	

SD: Standard deviation; BMI: Body mass index; TAH: Total abdominal hysterectomy; LVI: Lymphovascular invasion; BSO: Bilateral salpingo-oophorectomy; USO: Unilateral salpingo-oophorectomy; BPPLAND: Bilateral pelvic paraaortic lymph node dissection; OS: Overall survival

TABLE 2: Examination of the receptor expressions of the research group

	High grade serous n=46 n (%)	Low grade serous n=7 n (%)	Mucinous n=14 n (%)	Clear cell n=19 n (%)	p value
MUC1					
0	1 (2.2)	-	1 (7.1)	-	**<0.001****
1+	1 (2.2)	-	6 (42.9)	-	
2+	14 (30.4)	2 (28.6)	3 (21.4)	5 (26.3)	
3+	30 (65.2)	5 (71.4)	4 (28.6)	14 (73.7)	
MUC1 Group					
Low-stained	2 (4.3)	-	7 (50)	-	**<0.001****
High-stained	44 (95.7)	7 (100)	7 (50)	19 (100)	
HER2neu					
0	35 (76.1)	5 (71.4)	5 (35.7)	10 (52.6)	**0.002****
1+	10 (21.7)	2 (28.6)	2 (14.3)	6 (31.6)	
2+	1 (2.2)	-	2 (14.3)	1 (5.3)	
3+	-	-	5 (35.7)	2 (10.5)	
HER2neu group					
Low-stained	45 (97.8)	7 (100)	7 (50)	16 (84.2)	**<0.001****
High-stained	1 (2.2)	-	7 (50)	3 (15.8)	
ER					
Negative	5 (10.9)	1 (14.3)	14 (100)	13 (68.4)	**<0.001****
Positive	41 (89.1)	6 (85.7)	-	6 (31.6)	
PR					
Negative	22 (47.8)	1 (14.3)	14 (100)	16 (84.2)	**<0.001****
Positive	24 (52.2)	6 (85.7)	-	3 (15.8)	

*p<0.05; **p<0.001, chi-square and Fisher's exact test. ER: Estrogen receptor; PR: Progesterone receptor

sis. In the evaluation, it was found that several factors were more prevalent in patients with high staining of MUC1: lymph node metastasis, histological type of HGSOC, high grade, advanced stage, LVI, perioperative acid level >500 ml, and ER positivity. In patients with high HER2neu staining, factors such as premenopausal period, histological type of HGSOC, high grade, advanced-stage disease, and presence of LVI were observed. MUC1 expression was high in 95.4% of platinum-resistant and semi-resistant HGSOCs, whereas HER2neu was low. In ER-positive patients, several factors were observed to be higher, including post-menopausal status, mortality, presence of HGSOC histology, Grade 3, advanced-stage disease, LVI, and resection degree of R1 (Table 3). In patients with positive PR, the postmenopausal status and R1 resection degree were higher. Additionally, patients with positive PR had higher rates of advanced-stage disease, histological type of HGSOC, and grade 3 (Table 3).

Table 3 shows that 90.9% of 22 HGSOC patients with platinum-resistant and semi-resistant serous ovarian cancer tested positive for ER staining, with 13 of them also PR+. MUC1 was highly positive in 21 patients and HER2neu was low positive in 21.

In the study, patients survived an average of 64.8±6.2 months, but only 14.5±1.6 months without disease. The HGSOC group had an average survival time of 41.4±4.2 months, while the LGSOC group had an average survival time of 99.8±22.8 months. The MC and CCC groups had average survival times of 80.4±11.1 months and 75.9±13.7 months, respectively. Patients with the HGSOC type had lower survival rates compared to those with other histological types. Figure 2 shows the OS and DFS graphs of the patients according to the IHC staining results.

No significant difference was found in the DFS times of patients based on MUC1, HER2Neu, and ER. However, patients with positive PR had a lower DFS rate.

TABLE 3: Evaluation of the relationship MUC1 and HER2neu expression, estrogen and progesterone expression levels and clinical-pathological features and prognosis

	MUC1			HER2neu		
	Low n (%)	High n (%)	p value	Low n (%)	High n (%)	p value
Menopause						
Premenopause	3 (33.3)	27 (35.1)	0.918	23 (30.7)	7 (63.6)	**0.032***
Postmenopause	6 (66.7)	50 (64.9)		52 (69.3)	4 (36.4)	
Lymph node metastasis (+)	-	29 (45.3)	**0.036***	27 (43.5)	2 (22.2)	0.224
Histological type						
High grade serous	1 (11.1)	23 (29.8)	**<0.001****	24 (32)	-	**<0.001****
Low grade serous	-	7 (9.1)		7 (9.3)	-	
Platinum resistant-semi resistant serous	1 (11.1)	21 (27.2)		21 (28)	1 (9.1)	
Mucinous	7 (77.8)	7 (9.1)		7 (9.3)	7 (63.6)	
Clear cell	-	19 (24.7)		16 (21.3)	3 (27.3)	
Grade						
1	7 (77.8)	14 (18.2)	**<0.001****	16 (21.3)	5 (45.5)	**0.043***
2	-	12 (15.6)		9 (12)	3 (27.3)	
3	2 (22.2)	51 (66.2)		50 (66.7)	3 (27.3)	
Stage group						
Early	7 (77.8)	23 (29.9)	**0.004****	23 (30.7)	7 (63.6)	**0.032***
Late	2 (22.2)	54 (70.1)		52 (69.3)	4 (36.4)	
LVI (+)	1 (11.1)	54 (70.1)	**<0.001****	51 (68)	4 (36.4)	**0.041***
Resection degree						
R0	7 (77.8)	50 (64.9)	0.703	47 (62.7)	10 (90.9)	**0.022***
R1	2 (22.2)	25 (32.5)		27 (36)	-	
R2	-	2 (2.6)		1 (1.3)	1 (9.1)	
OS (month)	64.9±12.9	61.9±6.5	0.267	61.7±6.6	65.3±13.6	0.369
PFS (month)	17.6±6.4	14.3±1.2	0.798	14.9±1.7	11.1±4.4	0.234
	ER			PR		
	Negative n (%)	Positive n (%)	p value	Negative n (%)	Positive n (%)	p valuex
Menopause						
Premenopause	16 (48.5)	14 (26.4)	**0.037***	23 (43.4)	7 (21.2)	**0.036***
Postmenopause	17 (51.5)	39 (73.6)		30 (56.6)	26 (78.8)	
Lymph node metastasis (+)	8 (29.6)	21 (47.7)	0.132	19 (41.3)	10 (40)	0.915
Histological type						
High grade serous	3 (9.1)	21 (39.6)	**<0.001****	13 (24.5)	11 (33.3)	**<0.001****
Low grade serous	1 (3)	6 (11.3)		1 (1.9)	6 (18.2)	
Platinum resistant-semi resistant serous	2 (6)	20 (37.7)		9 (16.9)	13 (39.3)	
Mucinous	14 (42.4)	-		14 (26.4)	-	
Clear cell	13 (39.4)	6 (11.3)		16 (30.2)	3 (9.1)	
Grade						
1	14 (42.4)	7 (13.2)	**<0.001****	15 (28.3)	6 (18.2)	**0.018***
2	8 (24.2)	4 (7.5)		11 (20.8)	1 (3)	
3	11 (33.3)	42 (79.2)		27 (50.9)	26 (78.8)	
Stage group						
Early	21 (63.6)	9 (17)	**<0.001****	24 (45.3)	6 (18.2)	**0.010***
Late	12 (36.4)	44 (83)		29 (54.7)	27 (81.8)	
LVI (+)	15 (45.5)	40 (75.5)	**0.005****	32 (60.4)	23 (69.7)	0.381
Resection degree						
R0	29 (87.9)	28 (52.8)	**0.002****	43 (81.1)	14 (42.4)	**0.001****
R1	3 (9.1)	24 (45.3)		9 (17)	18 (54.5)	
R2	1 (3)	1 (1.9)		1 (1.9)	1 (3)	
OS (month)	69.6±8.7	54.2±6.9	0.041	61.7±6.6	65.3±13.6	0.029
PFS (month)	11.6±2.5	14.3±1.2	0.209	17.2±2.7	11.5±1.5	0.046

*p<0.05, **p<0.001; chi-square and Fisher's exact test; a: Independent student's t-test; b: Mann-Whitney U test. LVI: Lymphovascular invasion; OS: Overall survival; PFS: ER: Estrogen receptor; PR: Progesterone receptor

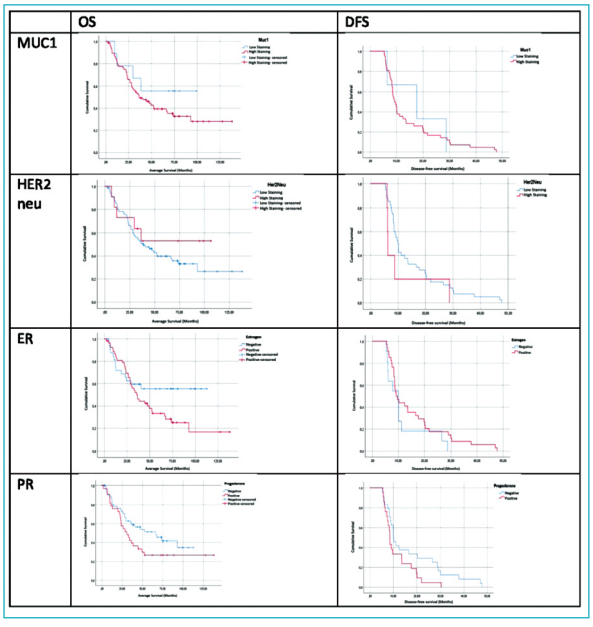

FIGURE 2: OS and DFS curves of the patients according to IHC staining results. OS: Overall survival; DFS: Disease-free survival; ER: Estrogen receptor; PR: Progesterone receptor

Table 4 analyzed factors affecting mortality using the multiple logistic regression model. The results showed that lymph node metastasis odds ratio [(OR)=3.500; 95% CI 1.264-9.688], advanced stage disease (OR=13.442; 95% confidence interval (CI) 4,599-39.288], grade 3 disease (OR=10,750; 95% CI 3.335-34.650), LVI (OR=21,296; 95% CI 6.797-66.724), perioperative ascites >500 ml (OR=81.200; 95% CI 9.745-676.626), platinum resistance (OR=46.588; 95% CI 1.126-234.578), ER positivity (OR=3.438; 95% CI 1.380-8.568), and optimal cytoreduction (OR=17.280; 95% CI 3.747-79.693) were determent-independent poor prognostic factors.

DISCUSSION

This study aimed to investigate the expression of HER2neu, MUC1, and estrogen and progesterone receptors that could produce treatment options in different EOC groups, and important results were obtained. High staining of MUC1 was remarkable in patients with HGSOC (95.7%), LGSOC (100%) and CCC (100%) histopathological types. In the MC group, 50% of the cases were HER2-neu positive. The highest ER positivity was observed in serous tu-

TABLE 4: Examination of the factors affecting mortality

	p value	OR	95% CI	p value
Age	0.110	1.033	0.993-1.074	0.107
Lymph node metastasis+	**0.013***	3.500	1.264-9.688	**0.016***
Advanced stage	**<0.001****	13.442	4.599-39.288	**<0.001****
Grade	**<0.001****			**<0.001****
Grade (1)		0.833	0.166-4.184	**<0.001****
Grade (2)		10.750	3.335-34.650	**<0.001****
LVI (1)	**<0.001****	21.296	6.797-66.724	**<0.001****
No peroperative ascites	**<0.001****			**<0.001****
Peroperative ascites <500 ml		10.150	2.702-38.125	**0.001****
Peroperative ascites >500 ml		81.200	9.745-676.626	**<0.001****
No platinum resistance	**<0.001****			0.999
Platinum semi resistant		31.359	5.796-374.484	**<0.001****
Platinum resistance		46.588	1.126-234.578	**0.001****
MUC1 positivity	0.304	2.069	0.514-8.334	0.306
HER2neu positivity	0.281	0.496	0.139-1.778	0.282
ER positivity	**0.007****	3.438	1.380-8.568	**0.008****
PR positivity	0.068	2.381	0.933-6.076	0.070
High grade serous	**<0.001****	9.257	2.836-32.548	**<0.001****
Low grade serous		0.084	0.014-0.514	**0.007****
Mucinous		0.084	0.021-0.337	**<0.001****
Clear cell		0.153	0.047-0.502	**0.002****
Optimal cytoreduction	**<0.001****	17.280	3.747-79.693	**<0.001****

*p<0.05, Multiple logistic regression analysis. OR: Odds ratio; CI: Confidence interval; LVI: Lymphovascular invasion; ER: Estrogen receptor; PR: Progesterone receptor

mors; all cases were negative for ER in MC. In total, 90.9% of 22 HGSOC patients with platinum-resistant and semi-resistant serous ovarian cancer tested positive for ER staining.

In our study, the majority of patients (87.2%) with EOC in our study had low staining for HER2neu. HER2neu staining was not frequently observed in patients with HGSOC and LGSOC. However, it is much more common in patients with MC and CCC. Numerous studies have shown that HER2neu amplification is common in ovarian cancers.[11-13] Høgdall et al. found a significant relationship between OS and HER2neu expression, with reduced OS as HER2neu expression increased.[12] Camilleri-Broët et al. observed in their study on 164 patients with advanced ovarian cancer that the HER2neu-positive group had shorter OS and DFS.[14] Similarly, we found that survival times decreased with increasing HER2neu expression level, although this finding was not statistically significant, potentially due to the small sample size. The literature has limited studies on the clinical significance of HER2neu. In a study of 320 patients with advanced ovarian cancer, no correlation was found between HER2neu status and various factors such as tumor stage, histological type, ascites, debulking status, age, and performance status. In the subgroup analysis of 109 patients with FIGO stage IIIc/IV primary tumor and suboptimal surgery, no significant association was found between HER2neu status and chemoresistance.[11] However, our study found a significant association between HER2neu and lower grade score, less LVI, and earlier disease stage, contradicting previous research. Despite this, we did not observe a significant difference in the survival times. Our study's' findings regarding the lack of a significant relationship between HER2neu level and platinum resistance and perioperative ascites level align with the existing literature. This indicates that the HER2neu status may not be a useful predictor of platinum resistance or the presence of perioperative ascites.

There is a lack of information about the potential prognostic value of MUC1 as a marker.[15] In this study, we found that MUC1 expression was high in 89.5% of patients and low in 10.5%. MUC1 was positively stained in all patients in the LGSOC and CCC groups, which is a significant finding. Both CCC and LGSOC patients are difficult to manage because of the limited treatment options, especially in relapsed cases. Our results suggest that MUC1 is a potential target for targeted therapies, and preclinical trials have shown promising results. However, clinical practice has not yet been initiated.[16] Future studies investigating the clinical efficacy of MUC1-targeted therapies in treating the LGSOC and CCC groups, which showed 100% positivity for MUC1 in our study, are warranted. MUC1 expression has been linked to tumor grade, stage, and prognosis in recent studies, indicating a potential role in tumor progression.[17] Our study confirmed this association, with a significant association between increasing MUC1 expression and the progression of tumor stage and grade. A study on ovarian tumors found that high expression of MUC1 was detected in 36 out of 45 malignant tumors, and a significant correlation was observed between high MUC1 expression and disease grade and stage, signifying that MUC1 is frequently associated with carcinomas as opposed to benign ovarian tumors.[15] Our study's' results were consistent with these findings, as patients with high MUC1 expression exhibited significantly advanced grades and stages, high rates of lymph node metastases, and LVI. In a study of 154 patients with ovarian cancer, MUC1 expression was found to be significant in terms of tumor grade, FIGO stage, and OS. High levels of MUC1 expression were detected in 106 patients, with serous being the most common histological subtype. Patients with positive MUC1 expression had a significantly longer OS than those with negative expression.[18] In contrast, we found no significant relationship between MUC1 expression and OS. Patients with high MUC1 expression had a lower 5-year DFS, which was statistically significant.

A significant proportion of ovarian cancers express estrogen and progesterone receptors either individually or together. While the frequency of receptors varies in different studies, with at least 62-77% for ER and 26-43% for PR, the differences may be due to variations in the immunohistochemical methods and cutoff values of the scoring systems.[19] In this study, 62% of the patients had positive ER and 38% had positive PR, which is consistent with the lit-

erature. A previous study reported negative ER expression in malignant mucinous tumors.[20] In a study evaluating histopathological differentiation and expression, the ER and PR positivity rates were investigated in 1,610 HGSOC, 95 LGSOC, 185 MC, and 354 CCC patients. The HGSOC group had a high ER positivity rate of 80.9% and a PR positivity rate of 27.8%. Similarly, the LGSOC group had a high ER positivity rate of 88.4% and a PR positivity rate of 56.8%. In contrast, the MC group had low ER (20.5%) and PR (15.6%) positivity rates, and the CCC group had similarly low ER (19.2%) and PR (7.9%) positivity rates.[21] Our study found that HGSOC patients had high ER and PR positivity rates (89.1% and 52.2%, respectively). In addition, 85.7% of the LGSOC patients were ER positive and 85.7% were PR positive. In accordance with the literature, ER and PR expressions were found to be negative in all of the MC patients in our study. Recent publications suggest that the expression of ER and PR, either alone or in combination, may have a positive effect on the OS of EOC patients.[21] Lindgren et al. found that PR was more important than ER in predicting prognosis and distinguishing histological type, and they attributed this to the inhibition of cell proliferation and induction of apoptosis in relation to progesterone.[22] A 2013 meta-analysis by Zhao et al. found that higher PR levels were linked to better survival rates.[23] However, the prognostic significance of increased ER levels was inconclusive. It is important to note that differences in tissue sampling and follow-up, selection of the most representative paraffin block, and clones of the selected primary antibodies may cause variations in the expression levels of the immunohistochemical stains in the tumor tissue. The impact of ER and PR positivity on ovarian tumor grade, stage, and survival has been investigated in various studies. Høgdall et al. conducted the "MALOVA"'' ovarian cancer study, which found that 36% of 582 patients with ovarian cancer had ER-positive tumors.[24] ER positivity was significantly associated with an increased FIGO stage, but no significant relationship was found between ER expression and tumor grade. However, a significant correlation was observed between ER expression and the amount of residual tumor after surgery. In the same study, 20% of the patients had PR-positive tumors, and high PR expression levels were significantly associated with an increased histological grade. Although there was no significant relationship between PR positivity frequency and increased FIGO stage, PR expression was significantly correlated with the amount of residual tumor after surgery. Our study showed a significant increase in both ER and PR positivity in the FIGO stage. We also observed a significant relationship between PR positivity and grade, similar to the MALOVA study.

There are several limitations to this study. First, benign cases were not included, making it difficult to fully understand the role of the markers in benign and malignant differentiation. Second, the sample size was small and non-homogeneous, which may have limited the statistical power of the study and its generalizability. Third, the literature poorly studied the relationship between the biomarkers and clinical parameters, which resulted in some limitations in the study's discussion. Fourth, variations in the immunohistochemical stains in the tumor tissue could have been caused by tissue sampling and follow-up, selection of the most representative paraffin block, and clones of the selected primary antibodies, which could have impacted the study findings'. Fifth, the study was retrospective, which could have restricted the ability to control for potential confounding variables. Therefore, many factors that may affect prognosis, such as the type of surgery, are different between the groups. Finally, the study was conducted at a single center, which may limit its application to other populations.

CONCLUSION

The results of our study may provide potentially important implications for the clinical management of patients in different EOC subgroups. High positive staining of MUC1 in the LGSOC and CCC groups, high ER/PR expressions in the platinum-resistant patients in the HGSOC group, and HER2neu positivity in half of the MC group are the significant findings of this study. To predict the response of HER2neu, MUC1, ER and PR expression levels to endocrine/target therapy, further studies with larger size and more homogeneous groups are needed.

These studies will contribute to the development of knowledge and experience about how targeted and individualized treatments can be beneficial in EOC subgroups.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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