Impact of sirtuin-1 expression on progression-free survival in non-endometrioid endometrial cancer: A retrospective cohort study

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Abstract. Sirtuin-1 (SIRT1) expression levels are upregulated in various types of cancer and are associated with adverse outcomes. However, there is limited research on SIRT1 expression in types of gynecological cancer. The present study primarily sought to investigate the expression characteristics of SIRT1 in non-endometrioid endometrial cancer (EC) using immunohistochemistry. The secondary endpoint was to evaluate the impact of SIRT1 expression levels on progression-free survival (PFS). The present study was a single-center, retrospective cohort study that included patients who underwent hysterectomy between June 2017 and December 2021 and had a postoperative histopathological diagnosis of non-endometrioid EC. The tissue slides were stained with a monoclonal antibody targeting the SIRT1 protein. The nuclear staining reaction of SIRT1 was considered to be positive in the presence of any percentage of nuclear staining. The cytoplasmic staining reaction of SIRT1 was assessed using the immune reactivity scoring (IRS) system, which was determined by multiplying the scores for the staining percentage and staining intensity. IRS values of 0 to 2 were considered as negative expression; 3 to 4 as low expression; 6 to 8 as moderate expression; and 9 to 12 as high expression. Cox proportional hazards regression models were used to identify factors influencing PFS. Data from a total of 43 patients who met the eligibility criteria were presented. Cytoplasmic staining with SIRT1 was detected in all samples (100%), whereas no nuclear staining was evident in any of the tissue samples. According to the IRS results, 20.9% of samples exhibited negative cytoplasmic expression, 14.0% exhibited low expression, 37.2% exhibited moderate expression and 27.9% exhibited high expression. The estimated 3-year PFS rate was 43.6%. Cox regression models demonstrated no independent factor influencing PFS. In conclusion, SIRT1 expression was found to be cytoplasmic in non-endometrioid EC. According to the IRS, ~80% of cases exhibited varying degrees of SIRT1 expression. However, SIRT1 expression levels had no significant impact on PFS.

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Introduction

Endometrial cancer (EC) represents the sixth most common cancer in women worldwide, accounting for 7% of all types of cancer and 4% of cancer-associated mortalities in women (1). A large proportion of patients present with an endometrioid histology, and the 5-year overall survival (OS) rate for patients with endometrioid type EC is >90% (2). By contrast, 15-20% of patients with EC exhibit non-endometroid histotypes, with a 5-year OS rate of ~70% in uterine-confined disease (3) and 50% in cohorts including patients with all stages (4).

The International Federation of Gynecology and Obstetrics (FIGO) stage has been consistently identified as the primary prognostic factor for patients with non-endometrioid ECs (3,4). Although age, lymphovascular space invasion (LVSI), lymph node dissection and adjuvant radiotherapy have been reported to be associated with disease-free survival (DFS) and/or OS, it is notable that there is considerable inconsistency between the results of the studies (3-5). Given that non-endometrioid ECs are more often associated with advanced disease and poor outcomes compared with endometrioid type ECs (5), there is a clear need to identify novel prognostic markers in this patient population to improve the disease outcomes.

In the past decade, numerous studies have demonstrated the prognostic value of molecular classification in patients with stage I to III EC (6-8). However, a recent study has shown that molecular classification had no effect on progression-free survival (PFS) or OS in patients with stage IV disease, and that OS was only influenced by tumor histotype and estrogen receptor status (9). There is growing evidence that expression of L1 cell adhesion molecule (L1CAM) may be a predictor of disease outcomes in patients with EC (10,11). A systematic

review and meta-analysis found that L1CAM overexpression was associated with a worse DFS (HR, 4.11) and OS (HR, 3.62), even in stage I EC (11). Despite the evidence that high L1CAM expression levels are associated with a higher FIGO grade and with older age (11), current understanding regarding the role of L1CAM in non-endometrioid ECs is still limited. This is partly due to the relatively small number of patients with non-endometrioid EC included in previous analyses (10,11).

Sirtuins (SIRTs) are a family of signaling proteins that regulate cellular functions and are encoded by the *Sir2* gene (12). SIRTs utilize oxidized nicotinamide-adenine dinucleotide as a catalyst and exhibit mono-ADP-ribosyl transferase or deacetylase activity, thus ensuring the proper functioning of cellular events such as metabolism, oxidative stress, transcription, apoptosis, DNA repair and inflammation (12). The SIRT protein family comprises seven different isoforms (SIRT1-7), which are distributed across various cellular compartments (13). SIRT1, SIRT6 and SIRT7 are considered to be nuclear proteins and show different subnuclear localizations, such as in heterochromatic regions and nucleoli. Conversely, SIRT3, SIRT4 and SIRT5 are typically found in mitochondria (14). Although the SIRT isoforms share a common catalytic core in terms of chemical and structural compositions, they show minor differences in the molecular structure of their active sites (13).

Sirtuin-1 (SIRT1) is mainly a nuclear protein but can translocate between the cytoplasm and nucleus in response to tissue and energy requirements (14). Several studies have reported that SIRT1 expression is upregulated and associated with poor disease prognosis in various types of cancer, including hepatocellular carcinoma, non-small cell lung cancer, breast cancer, gastric cancer, pancreatic cancer, colon cancer, prostate cancer, large B-cell lymphoma and acute myeloid leukemia (15,16). By contrast, a limited number of studies have investigated the correlation between the expression of SIRT1 and types of gynecological cancer, a large proportion of which includes cervical and ovarian cancer (17,18).

Understanding the expression patterns of SIRT1 in non-endometrioid EC and linking this to prognosis may help to tailor the need for adjuvant therapy, guide the identification of potential targeted therapies and improve patient outcomes. The present study aimed to investigate the expression characteristics of SIRT1 in patients with non-endometrioid type EC using immunohistochemistry. The secondary endpoint of the present study was to evaluate the prognostic impact of SIRT1 expression on PFS.

Materials and methods

Study design and patients. The present study was a single-center (Saglik Bilimleri University Antalya Training and Research Hospital; Antalya, Turkey), retrospective cohort study that included patients who underwent hysterectomy between June 2017 and December 2021, and had a postoperative histopathological diagnosis of non-endometrioid EC. Patients were excluded if they had an endometrioid histotype, a primary synchronous malignancy, insufficient clinical data or had poor-quality immunohistochemistry results.

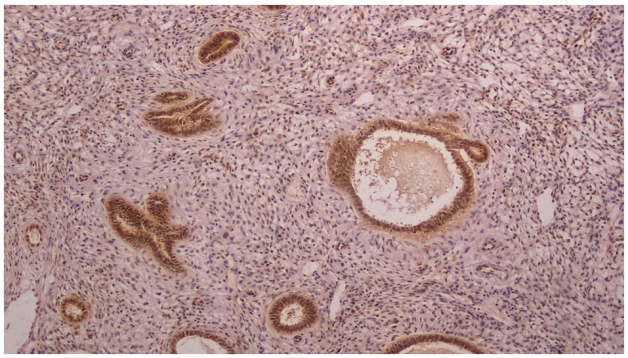

Figure 1. Representative images of sirtuin-1 cytoplasmic staining in cells lining normal endometrial glands (magnification, x200).

Following approval from the Ethics Committee of the Antalya Training and Research Hospital (approval no. 22/108; Antalya, Turkey), detailed clinical and pathological data of patients treated within the aforementioned study period were reviewed for eligibility. A total of 51 patients with non-endometrioid EC were identified. Of these, seven were initially excluded from the study as four had insufficient clinical data and three had a primary synchronous malignancy. Therefore, tissue samples from 44 patients were extracted from the pathology archives for immunohistochemical studies.

Immunohistochemical studies. The preparation of tissue samples for immunohistochemistry, including fixation, dehydration, embedding and sectioning was performed as previously described (19). Tissue sections (3 μm) were cut from tissue blocks onto pre-coated slides. The samples were subsequently incubated at 60˚C for 60 min, deparaffinised by passage through xylene (three times for 5 min) and rehydrated by successive immersion in 100, 96, 90, 80 and 70% alcohol for 5 min. A concentrated polymer-based protein-free blocking reagent (cat. no. TA-125-UB: Lab Vision™ Ultra V Block; Thermo Fisher Scientific, Inc.) was applied for 10 min at room temperature. Immunohistochemical staining was carried out using an automated platform (Shandon Pathcentre™; Thermo Fisher Scientific, Inc.) in accordance with the manufacturer's instructions, using a monoclonal mouse primary antibody that specifically targeted the SIRT1 protein (cat. no. ab110304; 1:1,000; Abcam). Then, a ready-to-use enzyme-labelled polymer secondary antibody (cat. no. TL-125-HL; UltraVision Large Volume Detection System HRP polymer; Thermo Fisher Scientific, Inc.) was applied for an additional 30 min at room temperature. Finally, the sections were stained with a diaminobenzidine (DAB) tetrahydrochloride substrate kit containing 25 ml of DAB solution and 250 ml of stable hydrogen peroxide substrate buffer (cat. no. 34002: DAB Substrate Kit; Thermo Fisher Scientific, Inc.) and with hematoxylin for counterstaining for 5 min each at room temperature.A gynecological pathologist, who was blinded to the clinical and pathological data, evaluated the staining reaction of the slides under a light microscope. The nuclear staining reaction of SIRT1 was considered to be positive in the presence of any percentage of nuclear staining. The cytoplasmic staining reaction of SIRT1 was assessed using immune reactivity scoring (IRS)

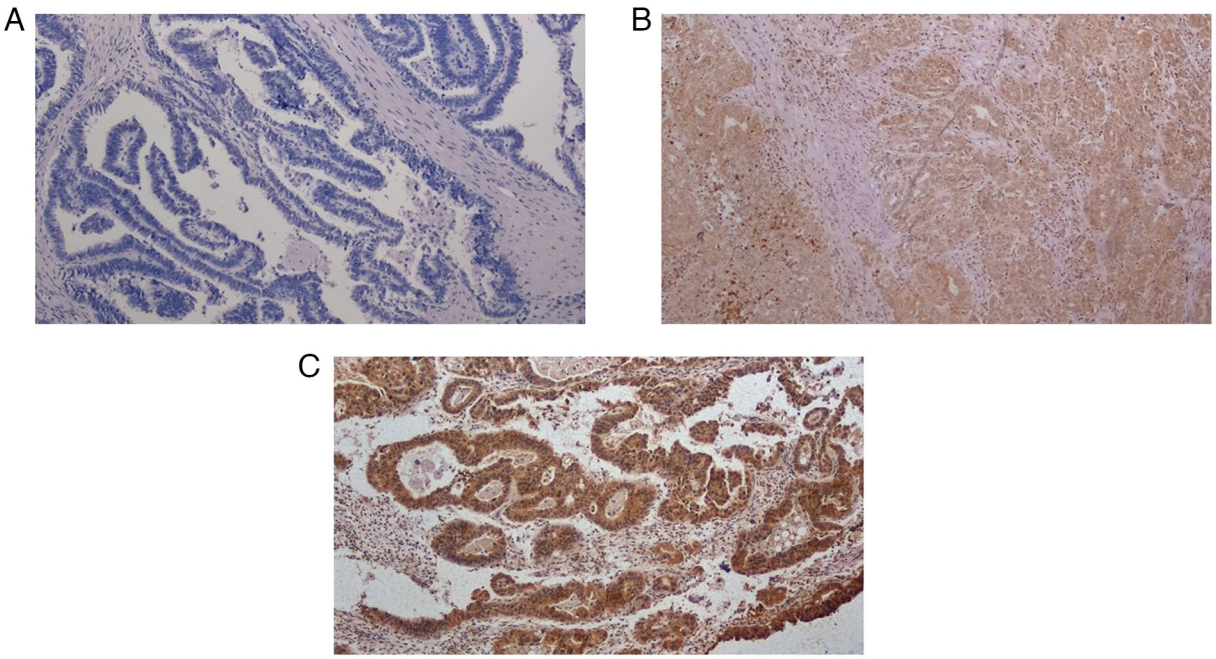

Figure 2. Representative images of cytoplasmic sirtuin-1 expression in cancer tissue samples with (A) no staining, (B) moderate staining and (C) strong staining (magnification, x100).

system (20). The percentage of cytoplasmic staining with SIRT1 was calculated as follows: Number of immunopositive cells divided by the total number of cells counted. The following criteria were used to grade the percentage of staining: 0, no staining; 1, ≤10%; 2, 11-50%; 3, 51-80%; and 4, ≥81%. The cytoplasmic staining in the cells that line the normal endometrial glands was used as a positive internal control for the intensity of the SIRT1 staining (Fig. 1). The staining intensity was graded semi-quantitatively as follows: 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining (Fig. 2).

The IRS values were determined by multiplying the scores for the staining percentage and staining intensity. Scores were graded as follows: 0-2, negative expression; 3-4, low expression; 6-8, moderate expression; and 9-12, high expression.

Statistical analysis. The analyses were carried out using SPSS (version 20.0; IBM Corp.) statistics software. Standard descriptive statistics were used, with counts and frequencies being utilized for binary variables and medians being supplemented by the range for continuous variables. Cox proportional hazards regression models with the enter method were used to evaluate the impact of SIRT1 and other clinical and pathological characteristics on PFS. The model results were presented as hazard ratios (HRs) with 95% confidence intervals (CI). P<0.05 was considered to indicate a statistically significant difference. Therefore, variables with a P-value <0.05 in univariate analyses were included in the multivariate analyses. PFS was defined as the period in months between the date of surgery and the date of disease progression, or relapse or mortality from any cause. The surviving patients that were not exhibiting progression or relapse were censored at the date they were last known to be alive according to the PFS data.

Results

Clinical and pathological characteristics. Of the 44 tissue samples that underwent immunohistochemical analysis in the present study, one was excluded from the final analyses due to poor quality immunostaining for evaluation. Therefore, data from a total of 43 patients were analyzed and presented.

Table I displays the surgical and pathological characteristics of included patients. The median age was 64 years. Of the 43 patients, six patients (16.4%) received neoadjuvant chemotherapy. A large proportion of patients (88.4%) had systematic lymph node dissection and 60.5% of patients had serous tumor histotype (pure serous or mixed with other histotypes). Deep (≥50%) myometrial invasion was observed in 60.5% of patients, LVSI in 65.1%, cervical invasion in 25.6%, adnexal involvement in 23.3% and lymph node metastasis in 47.4%. The distribution of FIGO stages was as follows: Stage I, 34.9%; stage II, 4.7%; stage III, 23.3%; and stage IV, 37.2%.

Disease outcomes of patients are summarized in Table II. Of the included patients, one patient succumbed to pulmonary thromboembolism on day 5 after surgery. Of the remaining patients, 95.2% received adjuvant chemotherapy with or without external beam radiotherapy. During a median follow-up time of 26 months, 22 of the 42 patients (52.4%) experienced disease progression. At the time of analysis, 20 patients (46.5%) were living with no disease, 5 (11.6%) were living with disease and 18 (41.9%) succumbed to the disease. The estimated 2-year and 3-year PFS rates were 50.0 and 43.6%, respectively, while the estimated 2- and 3-year OS rates were 65.7 and 62.4%, respectively.

Immunohistochemistry results. The immunohistochemical staining features of tissue samples with SIRT1 are presented in Table III. Cytoplasmic staining with SIRT1 was detected

Table I. Surgical and pathological characteristics of included patients.

Variables	Values
Median age, years (range)	64 (50-80)
Surgical procedure, n (%)	
TH/BSO plus staging surgery including lymphadenectomy	26 (60.5)
TH/BSO plus primary debulking surgery	11 (25.6)
Neoadjuvant chemotherapy followed by interval debulking surgery	6 (14.0)
Systematic lymph node dissection	38 (88.4)
Median no. of lymph nodes removed, n (range)	57 (16-107)
Median tumor size, cm (range)	4.4 (1-13)
Lymphovascular space involvement, n (%)	28 (65.1)
Deep (≥50%) myometrial invasion, n (%)	26 (60.5)
Cervical involvement, n (%)	11 (25.6)
Adnexal involvement, n (%)	10 (23.3)
Lymph node involvement, n (%)	18/38 (47.4)
Positive cytology, n (%)	10 (23.3)
FIGO stage, n (%)	
I	15 (34.9)
IA	11 (25.6)
IB	4 (9.3)
II	2 (4.7)
III	10 (23.3)
$IIIC_1$	4 (9.3)
$IIIC_2$	6 (14.0)
IVB	16 (37.2)
Tumor histotype	
Serous	19 (44.2)
Mixed (serous and endometrioid grade 3)	5 (11.6)
Mixed (serous and clear cell)	2 (4.7)
Mixed (endometrioid grade 3 and clear cell)	1 (2.3)
Clear cell	1 (2.3)
Carcinosarcoma	8 (18.6)
Dedifferentiated	5 (11.6)
Squamous cell	1 (2.3)
Mucinous	1 (2.3)

TH, total hysterectomy; BSO, bilateral salpingo-oophorectomy; FIGO, International Federation of Gynecology and Obstetrics.

Table II. Outcomes of patients.

Variables	Values
30-day postoperative mortality, n (%)	1 (2.3)
Adjuvant therapy, n (%)	40/42 (95.2)
Brachytherapy alone	2 (4.8)
Chemotherapy alone	16 (38.1)
Chemotherapy plus EBRT	22 (52.4)
Disease status on/after first-line therapy (primary surgery +/- adjuvant/ neoadjuvant therapy), n (%)	
Complete remission	35 (88.4)
Partial remission	6 (13.9)
Stable disease	1 (2.3)
Death	1 (2.3)
Recurrence in patients at complete remission, n (%)	15/35 (42.8)
Progression (disease recurrence, progression after partial remission or stable disease), n (%)	22/42 (52.4)
Median time to progression, months (IQR)	7 (3-13)
Median follow up time, months (IQR)	26 (13-45)
Survival status, n (%)	
Alive with no evidence of disease	20 (46.5)
Alive with disease	5 (11.6)
Dead of disease	18 (41.9)
Median progression-free survival, months (95% CI)	31 (6.7-55.2)
24, %	50.0
36, %	43.6
Median overall survival, months (95% CI)	65 (30.3-99.6)
24, %	65.7
36, %	62.4

EBRT, external beam radiotherapy; CI, confidence interval; IQR, interquartile range.

in all samples (100%), whereas no nuclear staining was evident in any of the tissue samples. According to the IRS, 20.9% of samples exhibited negative cytoplasmic expression, 14.0% exhibited low expression, 37.2% exhibited moderate expression and 27.9% exhibited high expression.

Cox regression analyses of factors influencing PFS. In the univariate analysis, five variables were significantly associated with PFS: Tumor size (P=0.026), deep (≥50%) myometrial invasion (P=0.029), lymph node involvement (P=0.001), positive peritoneal cytology (P=0.011) and FIGO stage (P<0.001). In the multivariate analysis, however, none of these variables remained an independent significant prognostic factor (Table IV).

Discussion

The present study investigated the expression characteristics of SIRT1 in non-endometrioid EC using immunohistochemistry; secondly, the effects of SIRT1 expression and various clinicopathological variables on the PFS of patients were examined. It was demonstrated that SIRT1 expression was found to be cytoplasmic in non-endometrioid EC. Additionally, according to the IRS, ~80% of cases had varying degrees of SIRT1 expression. Furthermore, the present study demonstrated that there were no independent factors examined that influenced PFS.

Table III. Immunohistochemical staining features of tumor cells with SIRT1.

Variables	No. of patients (%)
Cytoplasmic staining of tumor cells with SIRT1	43 (100)
Percentage of tumor-cell staining	
No staining	-
≤10	3 (7.0)
11-50	10 (23.3)
51-80	14 (32.6)
≥81	16 (37.2)
Staining intensity	
No staining	-
Weak	12 (27.9)
Moderate	18 (41.9)
Strong	13 (30.2)
Immune reactivity score	
0-2 (negative expression)	9 (20.9)
3-4 (low-expression)	6 (14.0)
6-8 (moderate-expression)	16 (37.2)
9-12 (high-expression)	12 (27.9)

SIRT1, sirtuin-1.

There are very few studies in the literature investigating SIRT1 expression in EC, most of which have focused on comparing the prevalence of SIRT1 expression between neoplastic and non-neoplastic endometrial tissues. Lin *et al* (21) demonstrated that SIRT1 expression was more prevalent in EC cells than in normal endometrial cells and that there was an association between SIRT1 expression and the levels of sterol regulatory element binding protein 1 (SREBP1), a nuclear lipogenic transcription factor. This study reported that SIRT1 knockdown could downregulate SREBP1 expression and suppress cell proliferation, and thus new therapeutic agents targeting SIRT1 may contribute to the treatment of EC (21). Similarly, Huang *et al* (22) investigated the effect of SIRT1-mediated LC3 acetylation on autophagy and proliferation of EC cells and reported that SIRT1 expression was higher in EC cells than in non-neoplastic endometrium. In EC cells overexpressing SIRT1, LC3 acetylation was inhibited, and cell proliferation was promoted whereas knockdown of SIRT1 inhibited proliferation, migration and invasion of EC cells (22). Bartosch *et al* (23) studied messenger RNA expression of SIRT1-7 in ECs and benign endometrial tissue samples using quantitative real-time PCR; it was found that, compared with benign tissues, ECs showed upregulation of SIRT7, whereas SIRT1, SIRT2, SIRT4 and SIRT5 were downregulated (23).

The number of studies investigating the relationship between SIRT1 expression and disease outcomes in EC is limited and the results are conflicting. Asaka *et al* (24) analysed SIRT1 expression in 108 cases of endometrioid EC and found that SIRT1 overexpression significantly increased the resistance of EC cell lines to cisplatin and paclitaxel. The authors reported that SIRT1 overexpression was significantly aligned with poor disease outcome (24). However, Al-Maghrabi and Al-Maghrabi (25) reported no association between SIRT1 overexpression and disease outcome in a study of 66 cases of endometrioid EC and five cases of serous EC. By contrast, Beyer *et al* (26) reported improved PFS and OS in cases with SIRT1 expression in a study involving 59 patients with endometrioid EC and six patients with clear cell EC. It was also reported that the staining intensity of SIRT1 was significantly higher in the endometrioid histotype in comparison to the clear cell histotype (26).

The studies by Al-Maghrabi and Al-Maghrabi (25) and Beyer *et al* (26) both included very few cases of non-endometrioid EC (n=5 and n=6, respectively), which is insufficient to draw conclusions on SIRT1 expression and survival in non-endometrioid EC. In the present study, no significant association between SIRT1 expression and PFS was demonstrated in a cohort consisting of only non-endometrioid ECs. To the best of our knowledge, this is the first study to characterize the expression patterns of SIRT1 and its association with prognosis exclusively in non-endometrioid ECs.

In the present study, SIRT1 was found to be expressed in the cytoplasm with no cases of nuclear expression. Similarly, Asaka *et al* (24) and Beyer *et al* (26) reported the location of SIRT1 expression as the cytoplasm. By contrast, Al-Maghrabi and Al-Maghrabi (25) reported outcomes related with nuclear expression of SIRT1. Furthermore, the scoring systems for SIRT1 expression used in the previous studies (24-26) differ from each other. Differences in the location of SIRT1 expression, scoring methods used and histotypes may explain the discrepancies between the results of the aforementioned studies (24-26).

The main strength of the present study was the analysis of the significance of SIRT1 expression in a homogeneous group of patients in terms of tumor histology, consisting exclusively of non-endometrioid cases. Given the aggressive nature of non-endometrioid ECs, it is evident that novel prognostic molecular markers are required to improve the management of patients with non-endometrioid EC. However, the literature on SIRT1 expression in EC consists of studies involving cases with endometrioid histology, either alone (24) or in combination with a limited number of non-endometrioid cases (25,26).

The analyses conducted in the present study have certain limitations. The present study was a retrospective analysis with a relatively small sample size. It included patients from a tertiary referral center, which limited the generalizability of the findings. Furthermore, the potential subjectivity in the interpretation of immunohistochemistry results could not be excluded due to the single center nature of the present study and the lack of external validation. The prognostic value of SIRT1 expression was only assessed through immunohistochemical techniques, and the results were not corroborated by molecular analysis. In addition, molecular classification was not used, which precludes definitive conclusions on the role of SIRT1 expression in different molecular subgroups. Over the past decade, evidence has emerged that there are at least four molecular subgroups of EC, each with a different prognosis (6-8). The subgroups included EC with a high mutation rate in the polymerase-ε (POLE) exonuclease domain (POLE-mutated), microsatellite-instability-high EC, EC with a low mutation rate and low somatic copy number alteration (non-specific molecular pattern EC, and EC with a low

Table IV. Factors associated with progression-free survival.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Age, years	1.029	0.976-1.084	0.292	-	-	-
Tumor size, cm	1.195	1.022-1.397	0.026[a]	-	-	0.615
Tumor histology			0.965	-	-	-
Serous (pure or mixed)	1.069	0.394-2.903	0.896	-	-	-
Carcinosarcoma	1.014	0.344-2.983	0.980	-	-	-
Dedifferentiated	2.040	0.598-6.957	0.255	-	-	-
Lymphovascular space involvement	0.605	0.265-1.383	0.234	-	-	-
Deep (≥50%) myometrial invasion	3.047	1.123-8.264	0.029[a]	-	-	0.970
Cervical involvement	1.546	0.654-3.652	0.321	-	-	-
Adnexal involvement	2.240	0.937-5.357	0.070	-	-	-
Lymph node involvement	8.337	2.388-29.107	0.001[a]	-	-	0.915
Positive peritoneal cytology	3.050	1.298-7.170	0.011[a]	-	-	0.682
FIGO stage	2.568	1.591-4.145	<0.001[a]	-	-	0.418
Stage I-II vs. III-IV	11.772	2.732-50.730	0.001[a]	-	-	-
Adjuvant therapy	1.533	0.205-11.438	0.677	-	-	-
No. of lymph nodes removed	1.015	0.994-1.037	0.154	-	-	-
Staining with sirtuin-1						
Percentage of staining	1.096	0.697-1.724	0.692	-	-	-
Intensity of staining	1.293	0.728-2.296	0.380	-	-	-
Immune reactivity score	1.046	0.934-1.172	0.435	-	-	-

[a]P<0.05. HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

mutation rate but high somatic copy number alteration rates and TP53 mutations. Therefore, the present study should be regarded as a preliminary investigation and further research with a larger cohort is essential to validate the results.

In conclusion, SIRT1 expression was found to be cytoplasmic in non-endometrioid EC. According to IRS results, ~80% of cases exhibited varying degrees of SIRT1 expression. However, SIRT1 expression did not significantly affect PFS.

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Availability of data and materials

The data generated in this study may be requested from the corresponding author.

Authors' contributions

NY conceptualized the study, collected, validated and analyzed the data and wrote the original draft. HTY conceptualized the study, designed the methodology and collected the data. AA, MuG, and MeG collected and interpreted the data. MeG contributed to the analysis and interpretation of the data. IU was the project administrator, contributed to the design of the study and critically reviewed the intellectual content. TT conceptualized the study, designed the methodology, validated and analyzed the data, and reviewed and edited the manuscript. NY and TT confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Antalya Training and Research Hospital (approval no. 22/108; Antalya, Turkey). Although the Ethics Committee waived the requirement for informed consent due to the retrospective nature of the study, written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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