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ORIGINAL RESEARCH

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Does coexistence of endometrial cancer and adenomyosis affect survival outcomes? A retrospective cohort study

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Abstract

The aim of this study is to investigate cancer survival parameters in patients with a combination of adenomyosis and endometrial carcinoma in pathological specimens. This is a retrospective cohort study conducted in a tertiary health center. Between January 2010 and December 2016, a total of 370 patients with a diagnosis of endometrial carcinoma who had undergone at least total abdominal hysterectomy and bilateral salpingoopherectomy. After excluding the patients from the pathology after reviewing the reports, 76 patients with adenomyosis were included in the study group and 287 patients without adenomyosis were included in the control group. The mean age of all patients was 63.6 $\pm$ 8.2 years. The mortality rate was 9.2% in patients with adenomyosis and 12.9% in patients without adenomyosis (p = 0.382). Overall, the mean time from diagnosis to death was 41.8 $\pm$ 24.7 months, which did not differ between patients with adenomyosis (29.3 $\pm$ 18 months) and without adenomyosis (44.6 $\pm$ 25.4 months, (p = 0.117). The presence of adenomyosis did not significantly affect overall survival (p = 0.434) or disease-free survival (p = 0.146). Median disease-free survival was 119 months in patients without adenomyosis and 120 months in patients with adenomyosis. None of the factors we studied affected survival in patients with adenomyosis. In our study, the presence of adenomyosis was found in 20.9% of patients who underwent hysterectomy for endometrial cancer, and this association had neither a positive nor a negative impact on disease prognosis, *i.e.*, mortality rate, disease-free survival and overall survival.

Keywords

Adenomyosis; Endometrial carcinoma; Prognostic factor; Survive

1. Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries [1]. Endometrial carcinoma, which is the fifth most common cancer worldwide, occupies a very important place as it is a major cause of morbidity and mortality. Its prevalence has increased over the years and accounts for approximately 4.8% of cancers in women [2]. The main risk factors are endogenous or exogenous uncontrolled estrogen exposure due to certain factors, including early menarche, late menopause, diabetes, obesity, nulliparity, advanced age ($\geq$55 years), and tamoxifen use [3]. In terms of cancer mortality, it ranks 14th [1]. Compared with other cancers associated with obesity, obesity appears to pose a higher relative risk for endometrial cancer [3]. The gradual increase in obesity suggests that endometrial cancer will increase seriously in the future, especially in developed countries. The average 5-year survival rate for all stages is about 80% [4]. The most important factor for prognosis is the histological grading of the cancer.

Adenomyosis is defined as the invasion of endometrial glands and stromal structures into the myometrium and usually occurs between the ages of 40–50 years [5]. Adenomyosis is traditionally diagnosed as an incidental finding in the pathology materials of women who have undergone hysterectomy for reasons such as chronic pelvic pain or abnormal uterine bleeding (AUB) [5]. Adenomyosis, along with cancer, is one of the most common histopathological findings diagnosed by pathologists when the uterus is removed during surgery and sent to pathology for examination [6]. Adenomyosis has been shown to be associated with various uterine and extrauterine pathologies with similar symptoms [7]. These pathologies include endometriosis, leiomyoma, endometrial polyps, and less commonly, endometrial hyperplasia and uterine malignancies [7]. In a study of 710 patients with adenomyosis who underwent hysterectomy, the presence of additional endometriosis alone (22.3%) or together with a fibroid (11.3%) was noted [8]. The incidence of adenomyosis in women with endometrioid adenocarcinoma ranges from 10% to 70% [9]. There is controversy in the

literature as to whether adenomyosis positively correlates with progression of endometrial carcinoma [10–12]. Numerous studies have reported that the coexistence of endometrial carcinoma and adenomyosis increases deep invasion of the myometrium [13, 14]. On the contrary, several studies suggested better prognosis, either due to a lower risk of nodal metastasis [10] or the fact that the disease is at an early stage when detected [15].

In this study, we aimed to compare the cancer survival parameters of patients with endometrial cancer patients with and without adenomyosis.

2. Materials and method

This retrospective cohort study was conducted in a tertiary center for gynecologic oncology in Ankara, Turkey. We first reviewed the medical records of 370 patients who had undergone at least one total abdominal hysterectomy with a definitive histopathologic diagnosis of endometrial cancer between January 2010 and December 2016. Patient records and information from the hospital information management system were retrospectively scanned as part of the study. Patients were screened from the death notification system of the Ministry of Health. Patients for whom there was death record in the system and who did not receive further treatment at our hospital were excluded. We excluded seven patients because they had discontinued follow-up in our hospital or the patient records were not accessible, because of the presence of another tumor with metastases in the endometrium, because of the presence of a synchronous tumor, or because of neoadjuvant chemotherapy. After reviewing the patients' pathology reports, 76 patients with adenomyosis were included in the study group and the remaining 287 patients without adenomyosis were included in the control group. In Turkey, there are about 3580 new cases of endometrial cancer annually. There are almost 100 gynecologic oncology centers in our country. Accordingly, about 30 new cases of uterine cancer are operated in each center annually. In the oncology clinic of our hospital, which is one of the largest centers in our city, the number of new applications per year is about 60. In this study, the period of 6 years was investigated. The number of 370 patients reviewed from the registry represents the total sample size for these years (for the years 2010–2016). However, patients who lost follow-up after surgery were excluded from the study. Therefore, our sample size was 363.

All histological sections were examined by two experienced pathologists in our hospital. For the diagnosis of adenomyosis, the presence of endometrial glands and stroma within the myometrium and at a distance of at least 4 μm from the endometrial junction was evaluated [16]. Parts of the uterus, the cervix, the lower uterine segment, and the uterus were divided into at least 6 parts, namely the anterior and posterior corpus, and each segment was examined in detail for the deepest tumor invasion.

The primary outcome of this study is to determine the frequency of coexistence of uterine cancer and adenomyosis. The secondary outcome is to determine the impact of this association on cancer survival.

We collected data on patients' descriptive demographic and clinical characteristics, including age, parity, body mass index, smoking, history of systemic comorbidities and medications, previous surgery, screening for known risk factors for endometrial cancer and risk groups (low-medium-high) [17], and history of infertility. We also retrieved clinical outcome data from the hospital information system: 5-year survival rate, recurrence-free survival, presence of recurrence, date of recurrence, site of recurrence, treatment of recurrence, date of last follow-up, and presence of mortality. Survival times and rates were calculated based on the time elapsed between the date of surgery and the date of death, recurrence, and last follow-up. We also evaluated preoperative and postoperative histopathologic findings: Probing/curettage, histopathologic diagnosis, depth of myometrial invasion, cervical stromal invasion, lymphatic invasion, adnexal involvement, presence of lymph node involvement, uterine leiomyoma or coexistence of endometriosis, presence of endometrial hyperplasia, presence of distant metastases, cytology positivity. Preoperative imaging findings (computed tomography, magnetic resonance imaging, ultrasound findings (double wall thickness of endometrium, presence of endometrial granules previously recorded in epicrisis)) and preoperative and postoperative histopathological findings (histopathological diagnosis, type of carcinoma, stage of disease, tumor diameter, tumor grade) pathology reports were evaluated and the information was recorded.

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) 24 (SPSS Inc., Chicago, IL, USA). Conformity to the normal distribution was assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests. The Yates correction and Fisher's Exact test were used to compare categorical variables by group. The Mann-Whitney U test was used to compare nonnormally distributed data by paired groups. Spearman's rho correlation coefficient was used to examine the relationship between non-normally distributed data. Factors affecting survival were assessed with Cox regression analysis. Adenomyosis-related factors were analyzed with logistic regression analysis. A Type I error level of 5% overall was used to derive statistical significance. Analysis results mean $\pm$ standard deviation for quantitative data. Categorical data as deviation and median (min–max) were presented as frequency (percentage). Comparison of categorical variables was performed with the chi-square test, and odds ratios were calculated. p values < 0.05 were considered statistically significant.

Sample size was calculated by power analysis based on the previous study by Aslan *et al.* [18]. In the t-test for independent samples with an α-value of 0.05, the power $(1 - \beta)$ was calculated to be 0.95 with 94 participants. Aslan *et al.* [18] determined the frequency of adenomyosis as the primary outcome in patients with endometrial carcinoma. These data were also used for power analysis (n = 103/552). For this reason, we believe that the effect size increases when our sample size is above this number.

3. Results

We found coexistence of endometrial carcinoma and adenomyosis in 76 (20.9%) patients. The mean age of all patients was 63.6 $\pm$ 8.2 years (32.0% of them were >60 years old),

and there was no difference between patients with and without adenomyosis. According to the endometrial cancer risk classification, 57.6% of patients were classified in the low-risk category, 41.3% in the intermediate-risk group, and 1.1% in the high-risk group. There was no significant difference between the distribution of risk groups in patients with and without adenomyosis ($p = 0.921$). Patients with and without adenomyosis also did not differ in body mass index, gravity, parity, history of infertility, smoking and comorbidities (Table 1).

Examination of tumor histology showed that endometrioid adenocarcinoma was most common in both groups, with no difference in this or other less common histologic subtypes ($p = 0.355$). Tumor histology examination of the study group revealed that 89.3% had endometrioid adenocarcinoma. While the rate of serous adenocarcinoma was 3.9% and clear cell adenocarcinoma was 2.9%, the rate of mucinous adenocarcinoma was 1.1%. In the study group, 62.5% of tumors were grade 1, 24.8% were grade 2, and 10% were grade 3. Tumor grade was similar in patients with adenomyosis and without adenomyosis ($p = 0.836$). Tumors detected in the study group were predominantly stage I tumors at a rate of 80.7%. There was no significant difference in tumor stage distribution between patients with adenomyosis and those without adenomyosis ($p = 0.997$). While 19.4% of the study group had no myometrial invasion, 53.6% had less than 50% invasion. Invasion detection rates were similar in patients with adenomyosis and without adenomyosis ($p = 0.443$). Cervical invasion was detected in 13% of patients, lymphatic space invasion (LVSI) in 18%, lymph node invasion in 9.6%, and distant metastasis in 3.6%. In addition to endometrial carcinoma, endometriosis was found in 1.9% of patients and endometrial hyperplasia in 20.9% of patients in the study group. The association of adenomyosis was significantly higher in patients with endometrial hyperplasia ($p < 0.001$). While uterine leiomyoma was detected in 48.7% of patients with adenomyosis, uterine leiomyoma was detected in 27.5% of patients without adenomyosis. The incidence of uterine leiomyomas was significantly higher in patients with concomitant adenomyosis ($p < 0.001$). The groups also did not differ with respect to other disease characteristics, except for a higher incidence of uterine leiomyoma (48.7% *vs*. 27.5%, $p < 0.001$) and endometrial hyperplasia (65.5% *vs*. 16.0%, $p < 0.001$) in patients with adenomyosis compared with those without adenomyosis (Table 2).

The mortality rate was 9.2% in patients with adenomyosis and 12.9% in patients without adenomyosis ($p = 0.382$). Overall, the mean time from diagnosis to death was 41.8 ± 24.7 months, which did not differ between patients with adenomyosis (29.3 ± 18 months) and without adenomyosis 44.6 ± 25.4 months, ($p = 0.117$). The presence of adenomyosis did not significantly affect overall survival ($p = 0.434$) or disease-free survival ($p = 0.146$). Median disease-free survival was 119 months in patients without adenomyosis and 120 months in patients with adenomyosis. None of the factors we examined affected survival in patients with adenomyosis (Table 3). Among the factors that influenced disease-free survival in these patients, Cancer antigen 125 (CA-125) level ≤35 IU/L was significantly associated with disease-free survival compared with those who had CA-125 level of >35 IU/L (Hazard Ratio (HR) 19.6, 95% Confidence Interval (CI) 1.60–238.9, $p < 0.02$; Table 4).

TABLE 1. Baseline characteristics of the study groups.

	Adenomyosis (+) (n = 76)	Adenomyosis (−) (n = 287)	*p*-value
Age (yr)			
Mean ± SD	62.71 ± 7.2	63.80 ± 8.2	0.266*
BMI (kg/m^2)			
Mean ± SD	33.4 ± 6.7	33.9 ± 6.5	0.668*
Gravity			
Median (min–max)	3 (0–15)	3 (0–15)	0.429***
Parity			
Median (min–max)	3 (0–8)	3 (0–9)	0.389***
History of infertility	0 (0%)	7 (2.4%)	0.156**
Smoking	14 (18.4%)	44 (15.3%)	0.513**
Comorbidities			
No	46 (60.5%)	149 (52.3%)	0.235**
HT	20 (26.3%)	71 (24.9%)	
DM	8 (10.5%)	41 (14.4%)	
DM and HT	2 (2.6%)	24 (8.4%)	
Endometrial cancer risk			
Low risk	45 (59.2%)	164 (57.1%)	0.921**
Intermediate risk	30 (39.5%)	120 (41.8%)	
High risk	1 (1.3%)	3 (1.0%)	

*BMI: Body mass index; HT: Hypertension; DM: diabetes mellitus; Data are shown as mean ± standard deviation (SD), median (minimum–maximum), and number (%). *Independent simple t test; **Chi Square test or Fisher's extract test; ***Mann Whitney U test.*

TABLE 2. Clinical disease characteristics of the study groups.

	Adenomyosis (+) (n = 76)	Adenomyosis (−) (n = 287)	*p*-value
Histology			
Endometrioid	64 (84.2%)	260 (90.6%)	
Serous	4 (5.3%)	10 (3.5%)	
Clear cell	2 (2.6%)	8 (2.8%)	0.360*
Mucinous	2 (2.6%)	2 (0.7%)	
Other	4 (5.3%)	7 (2.4%)	
Grade			
Grade 1	46 (67.6%)	169 (64.5%)	
Grade 2	15 (22.1%)	67 (25.6%)	0.840*
Grade 3	7 (10.3%)	26 (9.9%)	
Stage			
I	61 (80.3%)	232 (80.8%)	
II	5 (6.6%)	17 (5.9%)	0.990*
III	7 (9.2%)	26 (9.1%)	
VI	3 (3.9%)	12 (4.2%)	
Myometrial invasion			
No	18 (23.7%)	52 (18.3%)	
≤50%	39 (51.3%)	154 (54.2%)	0.440*
>50%	14 (18.4%)	67 (23.6%)	
Serosal involvement	5 (6.6%)	11 (3.9%)	
Cervical involvement			
Yes	6 (7.9%)	41 (14.3%)	0.140*
No	70 (92.1%)	245 (85.7%)	
Lymphovascular space invasion			
Yes	11 (14.5%)	54 (18.9%)	0.370*
No	65 (85.5%)	231 (81.1%)	
Lymph node involvement			
Yes	6 (7.9%)	30 (10.5%)	0.510*
No	70 (92.1%)	257 (89.5%)	
Distant metastasis			
Yes	2 (2.6%)	11 (3.8%)	0.610*
No	74 (97.4%)	275 (96.2%)	
Uterine leiomyoma			
Yes	37 (48.7%)	79 (27.5%)	<0.001*
No	39 (51.3%)	208 (72.5%)	
Endometriosis			
Yes	2 (2.6%)	5 (1.7%)	0.619*
No	74 (97.4%)	281 (98.3%)	
Endometrial hyperplasia			
Yes	46 (65.5%)	46 (16.0%)	<0.001*
No	30 (39.5%)	241 (84.0%)	

*Data are shown as number (%). *Chi Square test or Fisher's extract test.*

TABLE 3. Factors affecting survival in the presence of adenomyosis.

	p	HR	95% CI	
			Lower	Upper
Distant metastasis				
Yes	0.99	0.00	0.00	0.00
No				
Stage				
I–II	0.38	2.36	0.35	15.97
III–IV				
Grade				
Grade 1–2	0.99	0.00	0.00	0.00
Grade 3				
CA-125				
≤35 IU/L	0.86	1.23	0.12	12.80
>35 IU/L				
Histology				
Endometrioid	0.99	0.00	0.00	0.00
Others				
Age				
≤60 yr	0.69	1.44	0.24	8.52
>60 yr				

**Multivariate analysis. HR: Hazard Ratio; CI: Confidence Interval; CA-125: Cancer antigen 125.*

TABLE 4. Factors affecting disease-free survival in the presence of adenomyosis.

	p	HR	95.0% CI	
			Lower	Upper
Distant metastasis				
Yes	0.69	1.61	0.16	16.20
No				
Stage				
I–II	0.66	1.68	0.17	17.10
III–IV				
Grade				
Grade 1–2	0.20	4.45	0.46	42.76
Grade 3				
CA-125				
≤35 IU/L	0.02	19.57	1.60	238.85
>35 IU/L				
Histology				
Endometrioid	0.99	0.00	0.00	-
Others				

**Multivariate regression analysis. HR: Hazard Ratio; CI: Confidence Interval; CA-125: Cancer antigen 125.*

In patients with endometrial cancer, the survival rate was 94% for patients aged sixty years and younger and 85% for patients over 60 years. Age over 60 years proved to be a significant risk factor leading to a decrease in survival (HR: 2.43, $p = 0.031$). The survival rate in patients with adenomyosis was 87.1% and the survival rate in patients without adenomyosis was 90.8%. The presence of adenomyosis had no significant effect on survival (HR: 0.72, $p = 0.436$). CA-125 level above 35 IU/L proved to be a risk factor that significantly reduced survival (HR: 5.46, $p = 0.012$). The survival rate in patients with tumor histology of endometrioid adenocarcinoma was 89.2%. The fact that the tumor was endometrioid adenocarcinoma proved to be a factor that prolonged survival compared to the others (HR: 2.54, $p = 0.013$). Higher grade, tumor stage and the presence of distant metastases were found to be factors that shortened patient survival ($p = 0.018$, $p < 0.001$, $p < 0.001$, respectively) (Table 5).

4. Discussion

The clinical significance of the association of adenomyosis with endometrial cancer and its impact on prognosis have long been a controversial topic. In our study, the presence of adenomyosis was found in 20.9% of patients undergoing hysterectomy for endometrial carcinoma, and this association had neither a positive nor a negative impact on disease prognosis, *i.e.*, mortality rate, disease-free survival, and overall survival.

In the study evaluating the histopathological results of patients who underwent hysterectomy for various indications, it was found that leiomyomas were the most common with 51.2%, followed by adenomyosis with 20.5%, endometrial hyperplasia with 18.3%, and endometrial polyps with 5.9% [19]. In adenomyosis, the uterus grows diffusely and coexistence of uterine leiomyoma and adenomyosis is very common [19]. In our study, 76 of the patients we operated on for endometrial cancer had concomitant adenomyosis, and 48.6% of these patients had uterine leiomyoma and 2.6% had endometriosis. Leiomyoma is the most common benign tumor of the uterus and is detected in 20–77% of premenopausal women [20]. In our study, 32% of patients had leiomyoma and we found a significant association between the presence of leiomyoma and adenomyosis. The results of our study support the studies showing the association between adenomyosis and leiomyoma.

An association was found between many factors in etiology and the development of adenomyosis. One of the most strongly associated factors is pregnancy trauma [21, 22]. However, in our study, no significant association was found between parity, gravidity and the development of adenomyosis. These results support studies showing that there is no association between pregnancy and adenomyosis [23].

In studying the pathophysiology of endometrial cancer, many mechanisms that are common to adenomyosis stand out. Therefore, the presence of adenomyosis is thought to be a potential risk factor for the development of cancer [22]. It is suggested that the hyperestrogenic state that promotes the spread of adenomyosis to the myometrium may similarly promote the proliferation of endometrial cells and the development of estrogen-related endometrial cancer [11]. Another theory suggests that the auto-traumatization resulting from peristaltic contraction of the myometrium by adenomyosis triggers the chronic inflammatory response [21]. The resulting cytokines (interleukin (IL)-6 and IL-8), and growth factors (*e.g.*, vascular endothelial growth factor) likely promote tumor development and spread [18]. In both diseases, common mutations have been found in the signaling pathway that regulates cell proliferation [14]. Phosphatase and tensin homolog (PTEN) mRNA were decreased, particularly in adenomyosis [24]. Decreased transcription of this gene was also found in endometrial carcinoma [24]. Finally, there is evidence that adenomyosis converts directly to endometrial carcinoma [25].

Some studies have reported that the presence of adenomyosis in endometrial cancer is associated with a better prognosis [18, 26]. Adenomyotic foci have been found to have a different cytokine balance compared to normal endometrium [7]. It is known that the concentrations of interferon (IFN)-a, and IL-10 are increased in these foci [7]. These molecules are thought to have a protective effect on the progression of endometrial cancer due to their antitumor activities [21]. Similarly, the secretion of many cytokines is known to be decreased in these foci [7]. Since these cytokines play an important role in inflammation (IL-1b) and tumor progression (IL-8), decreased levels of oncogenic cytokines/growth factors in adenomyosis could theoretically attenuate the progression of endometrial cancer [13]. In contrast to these molecular-level studies, the results of our study show that the association of adenomyosis with endometrial cancer has no clinical impact on prognostic factors such as distant metastases and lymph node involvement and does not affect patient survival and mortality. Because of the similarities in etiopathogenesis, adenomyosis may co-occur with many endometrial and myometrial pathologies [27]. The most common concomitant pathologies are uterine fibroids (35–55%), endometrial polyps (2.3%), hyperplasia (10.5%), and adenocarcinoma of the endometrium (1.4%) [11]. Among these pathologies, endometrial glandular hyperplasia is a precursor lesion for type I endometrial carcinoma [11]. In the study by Taneichi *et al.* [28] it was found that the coexistence of endometrial hyperplasia and adenomyosis was more common compared to type I endometrial carcinoma [28]. When Isguder *et al.* [19] analyzed the pathology results of hysterectomy material, they found that leiomyomas were the most common at 51.2%, followed by adenomyosis at 20.5%, endometrial hyperplasia at 18.3%, and endometrial polyps at 5.9% [19]. In adenomyosis, the uterus grows diffusely and coexistence of uterine leiomyoma and adenomyosis is very common [5]. In our study, leiomyoma was found in 32% of patients and endometrial hyperplasia in 20.9% of patients. We found a significant association between the presence of endometrial hyperplasia and leiomyoma and adenomyosis.

Another hypothesis raised in studies suggesting a protective factor between adenomyosis and endometrial cancer is the mechanical protective function of the endometrial stroma in adenomyosis. The thickened endometrial stroma of adenomyosis prevents the progression of endometrial cancer invasion into the myometrium [29]. Although the greatest thickening in the foci of adenomyotic lesions occurs in the deep myometrial tissue, mild thickening may also occur in the subendothelial

TABLE 5. Factors affecting survival in uterine cancer.

Survival rates		Univarite		
		HR	95% CI	*p**
Age (yr)				
≤60	94.0%	2.43	1.08–2.43	0.031
>60	85.0%			
Body Mass Index (kg/m^2)				
≤30	84.6%	0.66	0.30–1.43	0.296
>30	88.4%			
Gravity				
Nulligravid	91.8%	1.47	0.52–4.11	0.464
Multigravid	87.3%			
Parity				
Nullipar	89.5%	1.13	0.47–2.67	0.781
Multiparous	87.6%			
CA-125 (IU/L)				
≤35	93.2%	5.46	1.45–20.53	0.012
>35	71.4%			
Histology				
Endometrioid	89.2%	2.54	1.21–5.30	0.013
Others	76.9%			
Grade				
Grade 1–2	91.6%	2.74	1.18–6.34	0.018
Grade 3	75.8%			
Stage				
I–II	91.1%	4.88	2.63–9.07	<0.001
III–IV	66.7%			
Distant metastasis				
No	89.1%	5.99	2.52–14.23	<0.001
Yes	53.8%			
Presence of adenomyosis				
Yes	90.8%	0.72	0.32–1.62	0.434
No	87.1%			

*HR: hazard rates. *Cox regression analyze.*

myometrial unit [30]. In the study by Musa *et al.* [31], the presence of adenomyosis was associated with low-grade tumor, less invasion of the myometrium, negative invasion of the lymphatic vascular space, and negative lymph node involvement. In the study by Matsuo *et al.* [32], endometrial cancer associated with adenomyosis was found to be less aggressive and survival was longer in patients with adenomyosis. Because the number of patients in both studies was small and the studies were retrospective, the results need to be supported by similar studies. The finding in our study that myometrial invasion, lymphovascular space invasion, and lymph node involvement did not change in the presence of adenomyosis does not seem to clinically confirm the findings in the literature.

Endometrial carcinoma is the most common gynecologic malignancy worldwide [29]. The most common histologic subtype is endometrioid adenocarcinoma [31]. In our study, endometrioid adenocarcinoma was the most common pathologic type with a rate of 89.3%, and the distribution rates were consistent with those of other studies [32–36]. Table 6 shows the rates of histopathologic types of endometrial carcinoma by study. A study by Musa *et al.* [31] found that the prevalence of adenomyosis in patients with endometrioid adenocarcinoma was significantly higher than other histologic types when histologic subtypes were compared. However, in our study, no significant difference was found in the distribution of tumor histology between patients with adenomyosis and those without adenomyosis ($p = 0.355$).

One of the limitations of the study is that because it was a retrospective study, it was difficult to obtain sufficient data

TABLE 6. An overview of the studies.

Study	Number	Adenomyosis n (%)	
		Yes	No
Koshiyama *et al*. [33]	179	29 (16.2%)	150 (83.8%)
Matsuo *et al*. [32]	571	271 (47.4%)	300 (52.5%)
Mao *et al*. [34]	127	24 (18.9%)	103 (81.1%)
Boonlak *et al*. [35]	350	132 (37.7%)	218 (62.3%)
Zouzoulas *et al*. [36]	229	64 (27.9%)	165 (72.1%)
Büyükşahin & Üstün	363	76 (20.9%)	287 (79.1%)

and some confounding factors could not be excluded. Another limitation is that the histopathologic examination was not repeated in detail with regard to adenomyosis and no assessment was made according to the severity of adenomyosis. In addition, different histotypes, stages, since endometrial carcinomas were analyzed together, this should be taken into account when evaluating the results. On the other hand, other histological subtypes were included so as not to reduce the sample size in a single center, although the largest cancer group is the endometrioid type.

5. Conclusions

In conclusion, the coexistence of adenomyosis and endometrial carcinoma has not been shown to have a positive or negative impact on survival in endometrial cancer. Larger studies are needed to better standardize other factors that influence survival and prognosis. In addition, to elucidate the pathophysiology, it is necessary to further the topic with molecular studies and to more clearly demonstrate the association between these diseases.

AVAILABILITY OF DATA AND MATERIALS

Data are openly available in a public repository that issues datasets with DOIs.

AUTHOR CONTRIBUTIONS

LGB, MCI, ACO, VK, SKA, YEU—contributed to project development, data collection, data analysis, and writing of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval was obtained by the institutional review board from Ankara Etlik Zubeyde Hanim Women's Health Training and Research Hospital on 12/16/2020 # 2020/170. Verbal and written informed consent were obtained from all participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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