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Does adenomyosis influence tumor characteristics and survival in endometrioid-type endometrial cancer??

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Abstract

Background The coexistence of adenomyosis and cancer of the endometrium has attracted heightened scrutiny, leading to inquiries regarding their possible interactions and clinical ramifications. This study sought to assess the influence of adenomyosis on tumor features and survival outcomes in patients with endometrioid-type endometrial carcinoma.

Materials and methods A retrospective cohort analysis was performed on 422 patients who underwent surgical intervention for endometrioid-type endometrial carcinoma. The cohort was categorized into two groups according to the presence or absence of adenomyosis. Clinical and pathological data were gathered and evaluated to compare tumor features and survival outcomes between the two cohorts.

Results Adenomyosis was present in 144 (34.1%) patients. Patients in the adenomyosis group demonstrated significantly higher gravidity and parity compared to those without adenomyosis. Lymphovascular space invasion was detected in 8.3% of the adenomyosis group compared to 17.6% in the non-adenomyosis group (a 53% reduction, $p=0.010$). Similarly, rates of myometrial invasion (81.3% vs. 65.5%, $p=0.001$), cervical stromal invasion (9.0% vs. 14.1%, $p=0.005$), and lymph node metastasis (4.2% vs. 14.4%, $p=0.001$) were significantly lower in patients with adenomyosis. The five-year overall survival rate was 90.8% in the adenomyosis group and 87.1% in the non-adenomyosis group, although this difference was not statistically significant ($p=0.689$).

Conclusions This study demonstrates that adenomyosis is associated with a significant reduction in aggressive tumor characteristics such as myometrial invasion, lymphovascular space involvement, and lymph node metastasis in patients with endometrioid-type endometrial cancer. These findings emphasize that adenomyosis may be a potential protective factor in endometrial cancer prognosis and should be considered in clinical risk assessment. Prospective studies with larger cohorts are needed to confirm the long-term effects of adenomyosis on survival.

Keywords Adenomyosis, Endometrial cancer, Endometrioid-type, Tumor characteristics, Survival outcomes

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Introduction

Endometrial cancer (EC) stands as a prevalent gynecologic malignancy, with its incidence steadily rising in recent decades [1, 2]. The intricate interplay of hormonal, metabolic, and genetic factors contributes to its development, with obesity, diabetes, and unopposed estrogen exposure recognized as key risk factors [3]. Amidst the diverse landscape of EC, endometrioid-type EC emerges as the most common histological subtype, often presenting with favorable prognostic characteristics [4].

Adenomyosis, a non-malignant disease marked by the presence of endometrial glands and stroma within the myometrium, is commonly observed in hysterectomy specimens of endometrial cancer patients [5–7]. The coexistence of these two entities has sparked considerable interest, prompting investigations into their potential interplay and implications for clinical management.

Numerous researches have investigated the influence of adenomyosis on the tumor features and prognosis of endometrial carcinoma, producing compelling albeit occasionally contradictory findings. While some studies suggest a potential protective role for adenomyosis, associating it with less aggressive tumor behavior and improved survival outcomes [2, 8–10], others have reported contrasting findings or no significant association [5, 6]. The underlying mechanisms through which adenomyosis might influence EC remain an area of active research, with proposed hypotheses encompassing inflammatory modulation, mechanical barriers, and early detection [2, 8].

This study aims to contribute to the ongoing dialogue regarding the relationship between adenomyosis and endometrioid-type EC. Through a thorough examination of the medical and pathologic characteristics in patients with and without adenomyosis, we want to clarify the possible influence of this cohabitation on tumor behavior and survival rates.

Materials and methods

This study was performed from January 1, 2001, to January 1, 2024, with 422 suitable patients who underwent surgery for endometrioid-type endometrial cancer at the Gynecological Oncology Clinic of the Department of Obstetrics and Gynecology, Mersin University Faculty of Medicine Hospital. The Mersin University Clinical Research Ethics Committee approved the protocol of this study on October 2, 2024, under decision number 2024/936.

The research study's criteria for inclusion were as follows: patients aged 18 years or older who underwent surgery for endometrioid type endometrial cancer without prior surgical intervention for endometrial cancer. Patients previously operated on for endometrial cancer, those with non-endometrioid type endometrial cancer, individuals with a history of chemotherapy or radiotherapy, patients with insufficient medical records, and individuals under 18 years of age were excluded from the study.

The demographic, clinical, and pathological data of the study participants were retrospectively acquired from patient records and the electronic patient registration system of Mersin University Hospital. All pathology specimens were assessed by experienced gynecopathologists in our institution's pathology department. The conclusive pathology reports of the patients were utilized to evaluate grade, tumor dimensions, amount of myometrial infiltration, lymphovascular space invasion, stromal and adnexal invasion, vaginal and parametrial invasion, pelvic and para-aortic lymph node metastasis, and distant metastasis. Patients who did not undergo pelvic and para-aortic lymph node dissection due to early-stage disease and who had no suspicion of metastasis in the abdomen or no metastasis reported in biopsies taken from intra-abdominal organs in the operation notes were considered to have no extrauterine metastasis (except lymph nodes) in their pathology results. No evaluation of lymphovascular space invasion (LVSI) was performed on preoperative endometrial biopsies, as this assessment was exclusively conducted on the final hysterectomy specimens due to the limited tissue sampling and potential sampling error inherent to preoperative biopsies.

In this study, the definitive diagnosis of adenomyosis was established by histopathologists based on the final pathological analysis of hysterectomy specimens, confirming the invasion of endometrial glands and stroma into the myometrium at least 2.5 mm beyond the endometrial-myometrial junction, or its identification in at least one low-power field. Although preoperative imaging modalities occasionally suggested the presence of adenomyosis, the determination of surgical staging and the formulation of the treatment strategy (including the extent of resection and lymph node assessment) were primarily guided by the assessed stage and grade of the suspected endometrial carcinoma, informed by intraoperative frozen section analysis. The suspicion of concomitant adenomyosis did not alter the established treatment approach. Non-aggressive histological types were defined as low-grade (Grade 1 and 2) endometrioid-type endometrial cancer, and aggressive histological types were defined as high-grade endometrioid-type endometrial cancer. Staging was performed according to the FIGO 2023 system. However, because of the retrospective nature of this study, molecular profiling could only be evaluated in a small subset of patients and was, therefore, excluded from the analysis.

The surgical team was apprised of the tumor's dimensions, the extent of myometrial penetration (less than or higher than 50%), and any cervical or adnexal

involvement as determined by intraoperative frozen section analysis. Lymph node dissection for surgical staging was conducted in patients with grade I-II endometrioid adenocarcinoma with a tumor diameter over 2 cm, myometrial invasion surpassing 50%, or cervical stromal involvement. In patients with grade III endometrioid adenocarcinoma, pelvic and para-aortic lymph node dissection was conducted without the use of a frozen section. Pelvic lymphadenectomy was not initially planned as a standalone procedure. In patients whose pre-operative imaging, specifically computed tomography (CT), magnetic resonance imaging (MRI) or Positron emission tomography–computed tomography (PET-CT) indicated a tumor diameter over 2 cm, pelvic lymphadenectomy commenced after dispatching the pathology specimen for frozen section analysis, without awaiting the results of the frozen section. However, in patients with grade I-II and myometrial invasion less than 50% on frozen section, para-aortic lymphadenectomy was not continued. In patients who underwent para-aortic lymph node dissection, the dissection was extended up to the level of the renal vein. Sentinel lymph node mapping was not routinely performed in our clinic during the study period, which is why it was not applied to patients with early-stage disease in this cohort.

The study data was analyzed using the SPSS 22.0 software package. Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as mean ± standard deviation, median, minimum and maximum. The normality of continuous variables was assessed utilizing the Kolmogorov-Smirnov test. The Student's t-test was employed to compare the means of two independent groups for variables exhibiting a normal distribution. The Mann-Whitney U test was employed for variables lacking a normal distribution. The associations among categorical variables were assessed with the Chi-Square test. Survival analysis was conducted using the log-rank test with the Kaplan-Meier curve. The threshold for statistical significance was established at $p < 0.05$ for all comparisons.

Table 1 Baseline characteristics of patients with and without adenomyosis

Variable	Adenomyosis		*p*
	Yes (*n* = 144)	No (*n* = 278)	
Age (year)	61.65 ± 10.61	61.00 ± 9.76	0.525
Gravity	4.0 (0–13)	3.0 (0–15)	0.000*
Parity	3.0 (0–10)	2.0 (0–11)	0.001*
BMI (kg/cm^2)	30.00 (26.0–35.0)	30.00 (26.0–35.0)	0.585
Laparoscopy	23 (16%)	50 (18%)	0.604
Laparotomy	121(84%)	228 (82%)	
Lymhadenectomy			
No	22 (15.3%)	38 (13.7%)	0.762
Pelvic	32 (22.2%)	70 (25.2%)	
Pelvic and para-aortic	90 (62.5%)	170 (61.2%)	

Results

A total of 422 patients were included in the study, with 144 (34.1%) patients diagnosed with adenomyosis. The mean age of the patients was 61.48 ± 10.14 years. No significant difference was observed in age or BMI between the groups. Obstetric history differed significantly between groups, with adenomyosis patients showing higher median gravidity (4.0 vs. 3.0, $p < 0.001$) and parity (3.0 vs. 2.0, $p = 0.001$) compared to those without adenomyosis. The majority of patients in both groups underwent laparotomy (84% vs. 82%), with no significant difference in the proportion of patients undergoing laparoscopy or laparotomy between the two groups (Table 1).

Patients with adenomyosis exhibited a significantly higher proportion of early tumor stages (IA1, IA2, IA3, IB, IC) compared to those without adenomyosis (77.8% vs. 58.6%), with an odds ratio of 2.47 (95% CI: 1.58–3.87, $p = 0.001$). Tumor grade was significantly different between the two groups, with a higher proportion of grade 1 tumors in patients with adenomyosis (79.2% vs. 65.8%, $p = 0.017$). The mean tumor size was 3.33 ± 1.84 cm, with a slightly smaller average tumor size in the adenomyosis group 3.03 ± 1.75 cm vs. 3.49 ± 1.88 cm, $p = 0.016$. Myometrial invasion was significantly less frequent in the adenomyosis group, with 81.3% of patients having less than 50% invasion compared to 65.5% in the non-adenomyosis group ($p = 0.001$). Lymphovascular space involvement was also significantly lower in the adenomyosis group (8.3% vs. 17.6%, $p = 0.010$). Cervical stromal invasion was detected in 9.0% of patients in the adenomyosis group, while 14.1% of patients in the non-adenomyosis group had cervical stromal invasion ($p = 0.005$) (Table 2).

The incidence of pelvic lymph node metastasis was significantly lower in patients with adenomyosis (4.2% vs. 14.4%, $p = 0.001$). No significant difference was found in the incidence of para-aortic lymph node metastasis between the two groups. However, patients with adenomyosis had a significantly lower incidence of adnexal metastasis (6.9% vs. 19.8%, $p = 0.001$), vaginal or parametrial involvement (0.7% vs. 5.8%, $p = 0.012$), and distant metastasis (1.4% vs. 11.9%, $p < 0.001$) compared to those without adenomyosis. The majority of patients in both cohorts underwent no lymphadenectomy, with no significant variations observed between the groups.

The 5-year overall survival rate was somewhat higher in the adenomyosis cohort (90.8%) than in the non-adenomyosis cohort (87.1%). Nevertheless, the log-rank test indicated no significant disparity in survival distributions between the two groups ($p = 0.689$, HR = 1.111, 95% CI: 0.66–1.86) (Fig. 1).

Table 2 Tumor characteristics and pathological findings in patients with and without adenomyosis

Variable	Adenomyosis		Odds Ratio (95% CI)*	*p*
	Yes (*n* = 144)	No (*n* = 278)		
Tumor stages				
stage IA1,IA2,IA3,IB, IC	112 (77.8%)	163(58.6%)	2.47 (1.58–3.87)	0.001*
stage IIA and higher	32 (22.2%)	115 (41.4%)		
Tumor grade				
1	114 (79.2%)	183 (65.8%)	1.97 (1.24–3.12)	0.017*
2	21 (14.6%)	67 (24.1%)		
3	9 (6.3%)	28 (10.1%)		
Tumor size (cm)	3.03 ± 1.75	3.49 ± 1.88		0.016*
Tumor size				
< 2 cm	34 (23.6%)	51 (18.4%)	1.37 (0.84–2.24)	0.207
≥ 2 cm	110 (76.4%)	226 (81.6%)		
Myometrial invasion				
< 50%	117 (81.3%)	182 (65.5%)	2.30 (1.44–3.69)	0.001*
≥ 50%	27 (18.8%)	96 (34.5%)		
Lymphovasculer space involvement				
No	132 (91.7%)	229 (82.4%)	0.43 (0.22–0.83)	0.010*
Yes	12 (8.3%)	49 (17.6%)		
Cervical stromal invasion				
No	131 (91.0%)	228 (82.0%)	0.45 (0.24–0.86)	0.014*
Yes	13 (9.0%)	50 (18.0%)		
Pelvic lymph node metastasis				
No	138 (95.8%)	238 (85.6%)	0.26 (0.11–0.62)	0.001*
Yes	6 (4.2%)	40 (14.4%)		
Paraaortic lymph node metastasis				
No	139 (96.5%)	262 (94.2%)	0.59 (0.21–1.64)	0.306
Yes	5 (3.5%)	16 (5.8%)		
Adnexal metastasis				
No	134 (93.1%)	223 (80.2%)	0.30 (0.15–0.61)	0.001*
Yes	10 (6.9%)	55 (19.8%)		
Vaginal or parametrial involvement				
No	143 (99.3%)	262 (94.2%)	0.12 (0.02–0.89)	0.012*
Yes	1 (0.7%)	16 (5.8%)		
Distant metastasis				
No	142 (98.6%)	245 (88.1%)	0.11 (0.03–0.44)	0.000*
Yes	2 (1.4%)	33 (11.9%)		

Discussion

This study examines the influence of adenomyosis on tumor features and outcomes for survival in patients with endometrioid-type carcinoma of the endometrium. Our findings indicate that adenomyosis may correlate with a more favorable oncological profile; however, this association did not yield a statistically significant enhancement in overall survival. These findings contribute to the ongoing discourse regarding the complex relationship between adenomyosis and endometrial cancer, offering insights that might influence clinical management and prognostication. These findings are consistent with several previous studies that have suggested a potential protective role for adenomyosis in the context of endometrial cancer [9, 10].

The mechanisms underlying this association remain an area of active research. One proposed mechanism is that adenomyosis may serve as a mechanical barrier, preventing or slowing tumor invasion into the myometrium [11, 12]. Another possibility is that the inflammatory microenvironment associated with adenomyosis may exert an anti-tumor effect [13–16]. Additionally, the presence of adenomyosis may lead to earlier detection of endometrial cancer, as women with adenomyosis may be more likely to undergo regular gynecological examinations due to symptoms such as abnormal uterine bleeding and pelvic pain [17, 18].

The interrelationship between adenomyosis and endometrial cancer appears to be significantly influenced by hormonal factors, particularly estrogen exposure. Similar to endometrial cancer, which is known to be associated

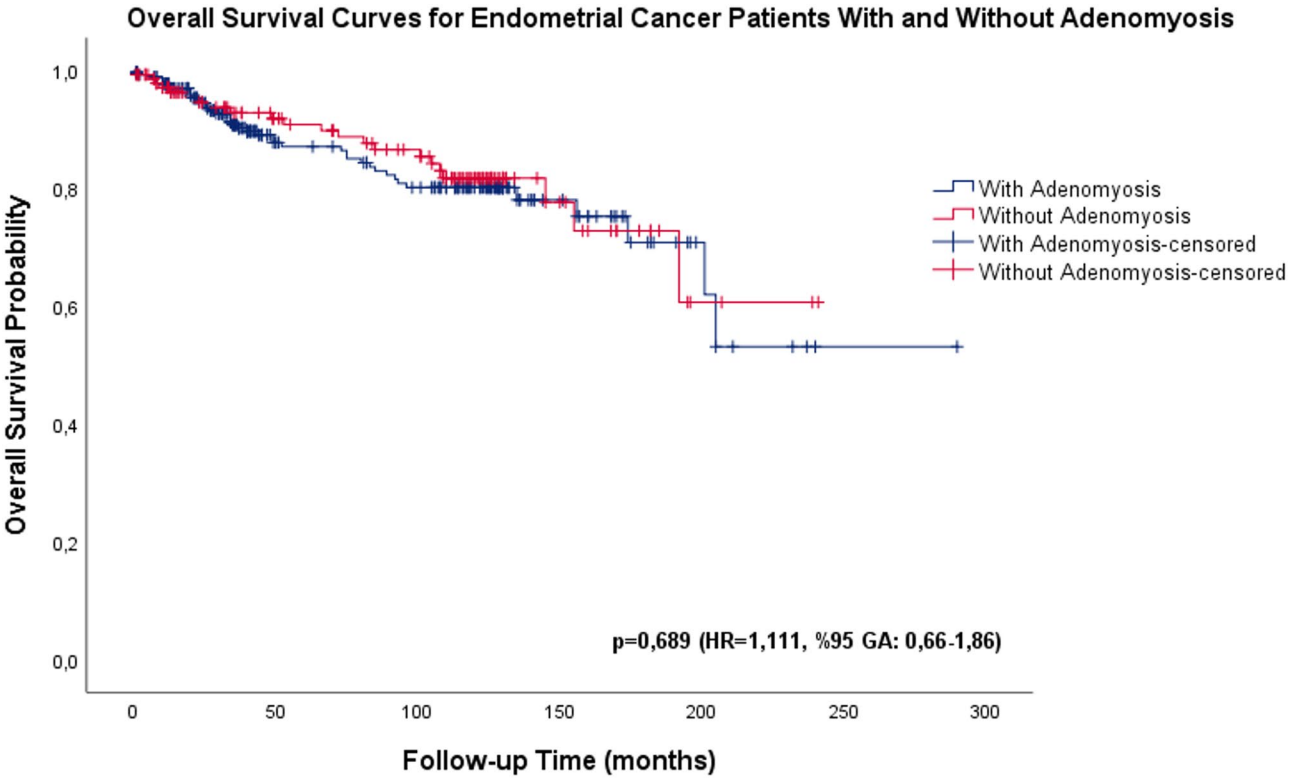

Fig. 1 Overall survival curve for the groups

with increased duration of endogenous estrogen exposure through early menarche, nulliparity, and late menopause, adenomyosis development is also linked to estrogen dominance [19]. Estrogen exposure is a recognized risk factor for both conditions, suggesting shared pathophysiological mechanisms [20]. Studies have demonstrated that prolonged exposure to estrogens, particularly when unopposed by progesterone, may represent a common pathway in the development of both adenomyosis and endometrial pathologies [21]. Hormone replacement therapy significantly impacts this relationship, with unopposed estrogen therapy substantially increasing endometrial cancer risk, while continuous progestin addition may reduce risk to levels even below those of non-hormone users [22]. The distinctive behavior observed between endometrial cancer co-existing with adenomyosis versus arising from adenomyotic foci suggests that the adenomyotic microenvironment may influence hormonal responsiveness and tumor phenotype [23]. Interestingly, women with adequate exposure to hormone therapy for endometriosis/adenomyosis treatment have shown decreased risk of endometrial cancer after extended follow-up, suggesting potential protective effects of certain hormonal treatments [24]. This complex hormonal interplay underscores the need for individualized risk assessment and careful consideration of hormonal therapy in women with adenomyosis, particularly when considering endometrial cancer risk profiles. Further prospective studies are warranted to elucidate the precise mechanisms through which hormonal exposures modulate the relationship between adenomyosis and endometrial cancer development.

This study's primary finding is the notable correlation between adenomyosis and a reduced probability of deep myometrial cell invasion and lymphovascular space involvement in endometrioid-type endometrial cancer. These pathological features are well-established indicators of aggressive tumor behavior and poor prognosis [4, 6, 7]. The reduced prevalence of these features in the adenomyosis group aligns with previous research suggesting a potential protective role for adenomyosis in endometrial cancer [2, 8, 10]. The observation of less frequent cervical stromal invasion in the adenomyosis group further supports the notion of a less aggressive tumor phenotype associated with adenomyosis. Cervical stromal invasion is a critical risk factor for metastases from lymph nodes and disease recurrence, and its diminished occurrence in the context of adenomyosis may enhance the excellent survival results seen in this cohort.

In our study, the adenomyosis group was associated with a lower likelihood of LVSI (8.3% vs. 17.6%, $p = 0.010$). The correlation between adenomyosis and diminished LVSI may be attributed to various reasons. The hypertrophied endometrial stroma in adenomyosis may impede

the penetration of endometrial carcinoma into the myometrium [10]. A distinct cytokine profile in adenomyosis might result in modifications to the local microenvironment, hence restricting tumor development and invasiveness [8]. These findings suggest that the presence of adenomyosis might indicate a less invasive potential of EC and a better prognosis.

The influence of adenomyosis on survival in endometrial cancer remains contentious, with certain research yielding contradictory findings or indicating no meaningful correlation [5, 6, 25]. Our results are largely concordant with the findings of recent meta-analyses and systematic reviews on this topic. Wang et al. (2023) indicated that adenomyosis correlated with enhanced overall and disease-free survival in patients with endometrial cancer [2]. An et al. (2020) similarly noted an elevated overall survival rate and a reduced incidence of deep myometrial penetration and lymphovascular space penetration in patients with adenomyosis [8]. These studies, along with our own, suggest a consistent pattern of less aggressive tumor behavior and potentially improved survival outcomes in the presence of adenomyosis.

However, it is important to acknowledge that the relationship between adenomyosis and endometrial cancer is not without controversy. Some studies have reported conflicting results, with adenomyosis being associated with a worse prognosis in certain cases [5, 6]. These discrepancies highlight the complexity of this association and the need for further research to unravel the underlying mechanisms.

While our findings demonstrated more favorable histopathological parameters in patients with adenomyosis, this did not translate into statistically significant survival benefits. Several factors may explain this apparent discrepancy. The follow-up duration (median of 5 years) may be insufficient to fully capture the long-term survival impact of adenomyosis, particularly considering the generally favorable prognosis of endometrioid-type endometrial cancer. The relatively low event rate in our cohort with high 5-year overall survival rates in both groups (90.8% vs. 87.1%) may have limited statistical power to detect meaningful differences. Treatment standardization between groups could have mitigated the potential survival advantage conferred by adenomyosis; patients in both groups received comparable surgical management and adjuvant therapies based on established risk factors, potentially equalizing outcomes despite differences in baseline tumor characteristics. Additionally, while adenomyosis appears to influence local tumor behavior, it may have less impact on other determinants of survival such as systemic disease progression or response to adjuvant therapies. These considerations highlight the need for larger prospective studies with extended follow-up periods and stratification by treatment modalities to better elucidate the relationship between adenomyosis and survival outcomes in endometrial cancer.

Our study possesses specific limitations that must be acknowledged when evaluating the results. The retrospective design inherent to our study carries the potential for selection bias and confounding. The omission of patients with non-endometrioid endometrial cancers restricts the applicability of our findings to other histological subtypes.

Future research should focus on prospective studies with larger cohorts and longer follow-up durations to validate our findings and explore the long-term impact of adenomyosis on survival in endometrial cancer. Additionally, investigations into the molecular mechanisms underlying the association between adenomyosis and endometrial cancer are warranted. A better understanding of these mechanisms could lead to the development of novel therapeutic strategies and prognostic tools for this disease.

In conclusion, our work presents evidence indicating that adenomyosis may correlate with less aggressive characteristics of tumors in patients with endometrioid-type carcinoma of the endometrium. These findings highlight the necessity of incorporating adenomyosis into the medical treatment and risk assessment of patients with this condition. Further research is necessary to confirm the long-term impact of adenomyosis on survival outcomes and to elucidate the molecular mechanisms underlying this association.

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Author contributions
GU, KA, AY and HY developed the concept and were responsible for data collection. SGG, GU and HA planned the study. GU, AY and HY analysed the results. GU, TTI and HA wrote the manuscript text and prepared figures and tables. All authors reviewed the manuscript for important intellectual content and approved the final version.

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Code usability
No datasets were generated or analysed during the current study.

Data availability
Can be used.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the guidelines of the Helsinki Declaration. Written informed consent was obtained from all participants. The study protocol was approved by the Clinical Research Ethics Committee of Mersin University Rectorate (with the ethics committee decision numbered 2024/936 dated 02/10/2024).

Approval for publication
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Competing interests
The authors declare no competing interests.

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