

# Southern Clinics of

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# Factors Affecting Disease Recurrence and Overall Survival in High-Grade Endometrial Cancer Patients

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**Keywords:** Disease recurrence; endometrial cancer; high-grade histology; overall survival; peritoneal cytology.



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## ABSTRACT

**Objective:** The main objective of present study was to determine the factors affecting disease recurrence and overall survival in patients with high-grade endometrial cancer.

**Methods:** The study retrospectively included women who underwent primary surgery between January 2017 and December 2021 and were diagnosed with serous, clear cell, carcinosarcoma, mixed type, grade 3 endometrioid or DE/undifferentiated endometrial cancer histology as documented in postoperative pathology reports. The data set was obtained from patient files and an electronic gynaecological oncology clinic database.

**Results:** A total of 81 patients were included in the analysis. 26 (32.1%) patients had recurrence. Pelvic lymph node positivity, para-aortic lymph node positivity, disease stage and adjuvant treatment were associated with disease recurrence. P values were 0.005, 0.009, 0.019, 0.002 and 0.009, respectively. Overall survival duration was 39 months. In multivariate analysis, only histotype (DE/undifferentiated, Hazard ratio (HR): 4.028 Confidence interval (CI): 1.208-13.434; P=0.023) and positive peritoneal cytology (HR: 3.719; CI:1.408-9.827; P=0.008) were significant independent prognostic factors for overall survival.

**Conclusion:** Histotype and positive peritoneal cytology may be associated with a worse overall survival in high-grade endometrial cancers.

## INTRODUCTION

Endometrial cancer (EC) is the most common gynaecological malignancy among women in developed countries, and an increasing trend has been observed over time. Typically, EC is diagnosed at an early stage due to the presence of early symptoms. The prognosis for this disease is generally favourable, with a 5-year survival rate of 96% when diagnosed at an early stage. However, the 5-year survival rate is reported to drop to 20% when diagnosed at a late stage.<sup>[1]</sup>

EC classification is traditionally based on histological features defined by Bokhman in 1983. Type 1 ECs are characterised as low-grade endometrioid ECs and are associated with conditions causing unopposed oestrogen production. In contrast, type 2 non-endometrioid ECs are defined as

high-grade tumours not associated with unopposed oestrogen production. The development of these tumours is typically characterised by atrophy and is frequently seen in older age groups.<sup>[2-4]</sup>

Following the publication of the Cancer Genome Atlas in 2013, the EC classification has been divided into four different subtypes based on molecular characteristics: POLE ultra-mutation, microsatellite instability, hypermutation, low copy number and high copy number.<sup>[5]</sup> This classification formed the basis for many subsequent studies, which identified subgroups using a molecular-based combination of immunohistochemistry and mutation analysis instead of genomic data. Nevertheless, this classification based on molecular characteristics is restricted, particularly in underdeveloped and developing countries where resources

are limited. Consequently, histological classification is still employed in many countries for staging and adjuvant therapies, which are based on this classification.

The majority of ECs account for approximately 80% of cases, are diagnosed at an early stage, and are characterised by low-grade endometrioid histotypes. High-grade endometrial cancers (HGEC) encompass the following histological grades: FIGO grade 3 endometrioid carcinomas, serous carcinomas, clear cell carcinomas, dedifferentiated/undifferentiated (DE/undifferentiated) carcinomas and carcinosarcomas. Although HGECs account for approximately 15-20% of all endometrial cancers, it is important to note that these histological subtypes are characterised by a high risk of relapse and are responsible for the majority of uterine cancer-related deaths, despite their low prevalence.<sup>[6,7]</sup>

The available literature has focused primarily on patients with low-grade endometrioid histology. However, given the aggressive nature of HGEC, there is an ongoing need to identify predictors of patient prognosis in clinical practice. The objective of this study was to determine the factors affecting disease recurrence and overall survival in patients with HGEC.

## MATERIALS AND METHODS

### Study Design

The present study comprises a retrospective cohort study of a single institution, including patients who had undergone surgery between January 2017 and December 2021. The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and approved by the Ethics Committee of Antalya Training and Research Hospital (approval date: 13 Jun 2024, approval number: 2024-172). As this was a retrospective study, the participants were not asked to provide informed consent prior to their involvement.

Following the approval of the ethics committee, a complete set of data was obtained from the patient charts and the hospital's electronic database. The data set included patient age, details of surgical procedures, tumor histotype, tumor size, the existence of lymphovascular space invasion (LVSI), myometrial invasion, involvement of lymph nodes, stage of the disease, the administration of adjuvant therapies, duration of follow-up, disease state and survival state at the date of final contact.

The patients included in the study were staged using the cancer staging system issued by the International Federation of Gynaecology and Obstetrics (FIGO) in 2009.

### Inclusion and Exclusion Criteria

The present study has been conducted on patients who undergo surgery, having at a minimum total hysterectomy plus bilateral salpingo-oophorectomy (TH/BSO), and were diagnosed with serous, clear cell, carcinosarcoma,

mixed type (endometrioid and non-endometrioid, with each component comprising a minimum of 10%), grade 3 endometrioid or DE/undifferentiated histology, as documented in the postoperative pathology reports.

Patients diagnosed with low-grade endometrioid histotype, synchronous malignancy, and an insufficient clinical data set were excluded from the study.

### Definition

The term "disease recurrence" is defined as the reappearance of imaging-proven disease following surgical intervention.

Overall survival (OS) was measured as the time from diagnosis to death, independent of cause, and patients who were alive at the most recent follow-up date were considered censored.

### Statistical analysis

Statistical analyses in the study were performed using the SPSS 27.0 (IBM Inc., Chicago, IL, USA) program. The assessment of normality was conducted using the Kolmogorov-Smirnov test, histogram analyses, skewness/kurtosis data, and Q-Q plot graphs. Quantitative variables were expressed as interquartile range (median [minimum – maximum]) or mean  $\pm$  standard deviation. Qualitative variables are expressed as frequency (N) and percentage (%). The Mann-Whitney U test or the independent t-test was employed to analyse the relationships between two independent groups. The investigation of relationships between qualitative parameters was conducted utilising Pearson's chi-square or Fisher's exact tests. Survival analyses were performed using the Cox regression method, and visual summarisation was performed with Kaplan-Meier curves. In the multivariate regression models, multicollinearity among variables has been checked. Multivariate analysis has been conducted in accordance with the 10 EPV (events per variable) rule. Throughout the study, the type-I error rate was based on 5% ( $\alpha=0.05$ ), and a  $p<0.05$  level was accepted as the significance limit with a confidence level of 95%.

## RESULTS

During the study period at our centre, a total of 93 patients were operated due to HGEC. Following a comprehensive evaluation of the data, it was decided to exclude 12 cases from the study. Nine patients were excluded due to missing follow-up information, and three patients were excluded due to death from postoperative complications. The final analyses were performed on a total of 81 patients who met the eligibility criteria.

Table 1 details the clinicopathological features of the patients. The median age recorded was 63.8 years. The majority of patients had grade 3 endometrioid and serous tumour histotype, with percentages of 33.3% and 30.8%, respectively. The majority of patients (76.5%) underwent

**Table 1.** The clinicopathological features of patients

	Distribution <sup>†</sup>		
Age, years	63.88±8.59		
Histotype			
Grade 3 endometrioid	27 (33.33%)		
Serous	25 (30.86%)		
Clear cell	2 (2.47%)		
DE/Undifferentiated	7 (8.64%)		
Mixt	11 (13.58%)		
Choriocarcinoma	9 (11.11%)		
Surgery			
TH/BSO alone	2 (2.47%)		
TH/BSO plus pelvic lymphadenectomy	9 (11.11%)		
TH/BSO plus pelvic -paraaortic lymphadenectomy	53 (65.43%)		
Debulking surgery	17 (20.99%)		
Cytology			
Negative	70 (86.42%)		
Positive	11 (13.58%)		
Myometrial invasion			
No	5 (6.17%)		
<50	24 (29.63%)		
≥50	52 (64.2%)		
Lymphovascular space involvement			
Negative	27 (33.3%)		
Positive	50 (64.94%)		
Paraaortic LN involvement			
Negative	65 (80.2%)		
Positive	16 (19.8%)		
Pelvic LN involvement			
Negative	54 (66.7%)		
Positive	27 (33.3%)		
Stage			
IA	21 (25.9%)		
IB	17 (20.9%)		
II	1 (1.23%)		
IIla	1 (1.23%)		
IIlb	0 (0%)		
IIlc1	11 (13.58%)		
IIlc2	9 (11.11%)		
IVa	3 (3.7%)		
IVb	18 (22.22%)		
Variable	Min.	Max.	Distribution <sup>†</sup>
Tumour size (cm)	0	22	4.4 (0.4-2)
Number of pelvic LN removed	0	69	27 (0-69)
Number of paraaortic LN removed	0	51	18 (0-51)
Total LN removed	0	110	49 (0-110)

<sup>†</sup>Qualitative data is expressed as frequency (N) and percentage (%). Quantitative variables are expressed as mean±SD or median (minimum–maximum)(IQR). IQR: Interquartile range; TH/BSO: Total hysterectomy plus bilateral salpingo-oophorectomy, LN: Lymph node.

systematic lymph node (LN) dissection in addition to TH/BSO. The mean number of LNs removed was 49. The positivity rate for the pelvic LNs was 33.3%, and the positivity rate for the para-aortic LNs was 19.8%. Deep myometrial invasion (defined as ≥50% of the myometrial invasion) was detected in 64.2% of cases, while the presence of LVSI was observed in 64.9% of cases. Moreover, the cytology positivity rate was 13.5%. The distribution of disease stages was as follows: Stage IA (25.9%), stage 4B (22.2%), stage IB (20.9%) and stage 3C1 (13.5%), according to frequency.

As shown in Table 2, the disease outcomes of the patients are presented. It is evident that a significant proportion of patients received adjuvant chemotherapy in isolation or in combination with external beam radiotherapy, with a percentage exceeding 77.78%. Following a median follow-up period of 39 months, it was observed that 26% of patients experienced disease recurrence. At the time of analysis, 31 patients (38.75%) were alive without disease, 3 patients (3.75%) were alive with disease, 33 patients (41.25%) had died of disease and 13 patients (16.25%) had died of other causes. The mean overall survival (OS) duration for the entire cohort was 39 months. In 2 cases, the disease remained undetected by imaging following treatment for recurrence. 3 patients died as a result of complications related with adjuvant treatment following primary treatment.

As shown in Table 3, factors associated with disease recurrence are presented. 26 (32.1%) patients had recurrence.

**Table 2.** Disease outcome of patients

	Distribution <sup>†</sup>
Adjuvant therapy	
No	3 (3.7%)
Brachytherapy alone	2 (2.47%)
EBRT +/- Brachytherapy	13 (16.05%)
Chemotherapy alone	22 (27.16%)
Chemotherapy + EBRT	41 (50.62%)
Recurrence	
No	50 (61.7%)
Yes	26 (32%)
Progression under treatment	5 (6.3%)
Survival	
Alive with no evidence of disease	31 (38.75%)
Alive with disease	3 (3.75%)
Dead of disease	33 (41.25%)
Dead of other reasons	13 (16.25%)
Recurrence-free survival (RFS)(months), IQR	12 (3–32)
Overall survival (months), IQR	39 (1–114)

<sup>†</sup>Qualitative data is expressed as frequency (N) and percentage (%). Quantitative variables are expressed as mean±SD or median (minimum – maximum). IQR: Interquartile range; EBRT: External Beam Radiation Therapy.

**Table 3.** Factors associated with disease recurrence

Variable	Recurrence		P-value
	No	Yes	
<b>Histotype</b>			
Grade 3 endometrioid	20 (40%)	7 (26.92%)	0.696 <sup>a</sup>
Serous	14 (28%)	8 (30.77%)	
Clear cell	2 (4%)	0 (0%)	
DE/Undifferentiated	3 (6%)	3 (11.54%)	
Mixt	6 (12%)	5 (19.23%)	
Choriocarcinoma	5 (10%)	3 (11.54%)	
<b>Surgery</b>			
TH/BSO alone	2 (4%)	0 (0%)	0.056 <sup>a</sup>
TH/BSO plus pelvic LA	8 (16%)	1 (3.85%)	
TH/BSO plus pelvic -paraaortic LA	35 (70%)	17 (65.38%)	
Debulking surgery	5 (10%)	8 (30.77%)	
<b>Cytology</b>			
Negative	46 (92%)	20 (76.92%)	0.082 <sup>a</sup>
Positive	4 (8%)	6 (23.08%)	
<b>Myometrial invasion</b>			
No	3 (6%)	2 (7.69%)	0.075 <sup>a</sup>
<50	20 (40%)	4 (15.38%)	
≥50	27 (54%)	20 (76.92%)	
<b>Lymphovascular space involvement</b>			
Negative	21 (42.86%)	6 (24%)	0.111 <sup>b</sup>
Positive	28 (57.14%)	19 (76%)	
<b>Paraaortic LN involvement</b>			
Negative	44 (88%)	17 (65.38%)	0.019 <sup>b</sup>
Positive	6 (12%)	9 (34.62%)	
<b>Pelvic LN involvement</b>			
Negative	39 (78%)	12 (46.15%)	0.005 <sup>b</sup>
Positive	11 (22%)	14 (53.85%)	
<b>Stage</b>			
IA†	18 (36%)	3 (11.54%)	0.002 <sup>a</sup>
IB †	15 (30%)	2 (7.69%)	
II	1 (2%)	0 (0%)	
IIIa	1 (2%)	0 (0%)	
IIIb	0 (0%)	0 (0%)	
IIIc1	6 (12%)	5 (19.23%)	
IIIc2 †	3 (6%)	6 (23.08%)	
IVa	1 (2%)	1 (3.85%)	
IVb †	5 (10%)	9 (34.62%)	
<b>Adjuvant therapy</b>			
No	1 (2%)	0 (0%)	0.009 <sup>a</sup>
Brachytherapy alone	2 (4%)	0 (0%)	
EBRT +/- Brachytherapy†	13 (26%)	0 (0%)	
Chemotherapy alone	10 (20%)	9 (34.62%)	
Chemotherapy + EBRT	24 (48%)	17 (65.38%)	

Variables are expressed as frequency (N) and percentages (%). <sup>a</sup>Subcategories with significant proportion differences between the recurrence groups have been marked. LA: lymphadenectomy; LN: Lymphnode(s); TH/BSO: Total hysterectomy plus bilateral salpingo-oophorectomy; EBRT: External Beam Radiation Therapy. <sup>†</sup>Fisher's exact test, <sup>b</sup>Pearson chi-square analysis.

**Table 4.** Univariate cox regression analysis in terms of OS

Variables	Univariate		P-value
	HR	95% CI	
Age (years)	1.051	1.006–1.098	0.025
Tumour size (cm)	1.027	0.930–1.134	0.062
Total LN removed	0.991	0.968–1.014	0.426
Histotype			
Grade 3 Endometrioid (ref)			
Serous	2.094	0.774–5.667	0.146
DE/Undifferentiated	5.55	1.773–17.367	0.003
Mixt	2.214	0.622–7.886	0.220
Choriocarcinoma	2.645	0.805–8.697	0.109
Surgery			
TH/BSO + pelvic LA (ref)			
TH/BSO + pelvic–paraaortic LA	1.224	0.285–5.255	0.786
Debulking surgery	3.531	0.787–15.847	0.004
Peritoneal cytology (positive)	2.794	1.250–6.249	0.012
Myometrial invasion (overall)	1.621	0.834–3.149	0.154
Lymphovascular space involvement	3.31	1.348–8.131	0.009
Pelvic LN involvement	2.938	1.475–5.853	0.002
Paraaortic LN involvement	2.166	1.037–4.523	0.004
Stage			
Ia (ref)			
Ib	0.365	0.041–3.266	0.367
II	-	-	0.987
IIIa	-	-	0.986
IIIc1	5.221	1.467–18.585	0.011
IIIc2	3.577	0.952–13.447	0.059
IVa	10.654	2.350–48.314	0.002
IVb	7.109	2.315–21.834	0.001
Adjuvant therapy (overall)	1.122	0.771–1.632	0.547

Hazar ratio; CI: Confidence interval; ref: reference subcategory; LA: Lymphadenectomy; LN: Lymph node; TH/BSO: Total hysterectomy plus bilateral salpingo-oophorectomy; OS: Overall survival.

The presence of pelvic LN positivity, para-aortic LN positivity, stage of disease and adjuvant therapies have been associated with disease recurrence. The P values were 0.005, 0.009, 0.019, 0.002 and 0.009, respectively.

In univariate analysis, eight variables were significantly related with OS: Age (P=0.025), histotype (DE/undifferentiated, P=0.003), debulking surgery (P=0.004), positive peritoneal cytology (P=0.012), LVSI (P=0.009), pelvic LN positivity (P=0.002), paraaortic LN positivity (P=0.004) and FIGO stage (Stage IIIc1, P=0.001; IVa, P=0.002; IVb, P=0.001) (Table 4). However, multivariate analysis revealed that only histotype (DE/undifferentiated, Hazard ratio (HR): 4.028 Confidence interval (CI): 1.208–13.434 P=0.023) and positive peritoneal cytology (HR: 3.719, CI: 1.408–9.827 P=0.008) were independent significant prognostic factors for OS. Table 5 detailed the independent prognostic factors in multivariate analyses.

## DISCUSSION

The present study aims to analyse the factors that affect disease recurrence and OS in patients diagnosed with HGEC. The study demonstrated that the presence of pelvic LN positivity, para-aortic LN positivity, stage of disease and adjuvant therapies have been associated with disease recurrence. Furthermore, the study revealed that histotype and positive peritoneal cytology are independent factors influencing OS.

A review of the literature indicates the presence of several factors associated with OS in patients diagnosed with HGEC.<sup>[8-10]</sup> In a recent study by Lu et al.,<sup>[11]</sup> 3,933 patients with serous, clear cell, carcinosarcoma and mixed EC were analysed using The Surveillance, Epidemiology, and End Results (SEER) database. The study found that factors such as race, tumour size, histotype, stage, exami-

**Table 5.** Multivariate cox regression analysis in terms of OS

Variables <sup>†</sup>	Univariate		P-value
	HR	95% CI	
Dimensional Reduction <sup>§</sup>			
Age	1.521	1.064–2.176	0.022
Lymphovascular space involvement			
Pelvic LN involvement			
Para-aortic LN involvement			
Histotype			
Grade 3 Endometrioid (ref)			
Serous	13.434	0.476	
DE/Undifferentiated	13.434	0.023	
Mixt	10.302	0.107	
Choriocarcinoma	10.566	0.105	
Peritoneal Cytology (positive)	3.719	1.408–9.827	0.008

<sup>†</sup>Surgery and Stage variables are excluded in the multivariate model due to high multicollinearity issues. <sup>§</sup>Due to fact that the primary output/event sample size is insufficient, dimensional reduction has been applied for 4 variables to meet the  $\geq 10$  EPV (Events per variable) assumption. These merged variables are used for adjustment purpose only. HR: Hazard ratio; LN: Lymph node; CI: Confidence interval; ref: reference subcategory; OS: Overall survival.

nation of para-aortic lymph nodes, examination of pelvic lymph nodes, surgery, lung metastasis, radiation therapy and chemotherapy were found as independent risk factors for poor OS ( $P < 0.001$ ). The present study has a number of points of agreement with the abovementioned study. However, due to an inadequate sample size, it was not possible to subject some factors (e.g. LVSI, pelvic LN positivity, para-aortic LN positivity) to multivariate analyses alone. It was only the histotype associated with OS as an independent risk factor that demonstrated a similarity to the abovementioned study.

LVSI is described as the existence of tumour cells in lymphatic vessels or small blood vessels away from the primary tumour. The 5-year recurrence rate is higher in patients with EC who are LVSI positive, and the LVSI positivity is the most potent independent prognostic factor for pelvic regional recurrence, distant metastasis and OS.<sup>[12-14]</sup> In a recent study conducted by Li et al.,<sup>[15]</sup> the analysis of 392 low-grade and 138 HGEC cancer patients was undertaken, and the study found that LVSI positivity was identified as an independent risk factor for recurrence for HGEC patients ( $P = 0.001$ ). In the present study, no significant correlation was identified between LVSI positivity and disease recurrence. Unfortunately, the study could not identify LVSI positivity as an independent risk factor for OS due to limited sample size.

Despite the clear association between HGECs and poor survival and high recurrence rates, the findings of studies examining whether there are differences in survival and recurrence between sub-histotypes of HGEC are inconsistent. A study by Ayeni et al.<sup>[8]</sup> failed to identify any statistically significant disparities in OS between grade 3

endometrioid, serous, and clear cell carcinomas. Furthermore, Suarez et al.<sup>[2]</sup> discovered that there was no discrepancy between carcinosarcoma, clear cell and serous EC patients with regard to recurrence-free survival and disease-specific survival. However, a recent study by Lee et al.<sup>[16]</sup> and Scharl et al.<sup>[17]</sup> found that carcinosarcoma was associated with a higher rate of recurrence and poorer survival outcomes in comparison to other sub-histotypes of other HGEC. Similarly, Öztürk et al.<sup>[18]</sup> found that the accuracy of predicting FIGO stage before and after surgery for prognosis in HGEC is of critical importance and highlighted the aggressive behaviour of certain histotypes. In the present study, sub-histotypes were not found to be associated with disease recurrence. However, de/undifferentiated tumours were identified as an independent risk factor associated with poorer survival. The most significant reason for the observed discrepancy in outcomes between the present study and other studies is believed to be the exclusion of DE/undifferentiated tumours from statistical analysis as a discrete sub-histotype in the abovementioned studies.

In the 2009 revision of the cancer staging system by FIGO, positive peritoneal cytology was no longer accepted as a stage-defining variable due to the existence of studies that failed to prove the role of positive peritoneal cytology in the survival of patients with endometrial cancer and its false negativity ranging from 23% to 52%.<sup>[19-21]</sup> The FIGO staging system was revised in 2023, yet peritoneal cytology remains excluded from the staging criteria.<sup>[22]</sup> Nevertheless, given the uncertain prognostic significance of positive peritoneal cytology as demonstrated by numerous studies, the National Comprehensive Cancer Network (NCCN) Guidelines advocate the collection of peritoneal cytology

during endometrial cancer staging surgery.<sup>[23]</sup> In a recent study, Sakai et al.<sup>[24]</sup> undertook a retrospective analysis of 74,984 patients, including 18,825 HGEC. The study found that positive peritoneal cytology was associated with both more recurrences and worse OS. Furthermore, in a retrospective study of 101 patients with early-stage serous and clear cell carcinoma, Yang et al.<sup>[25]</sup> found that positive peritoneal cytology was independently associated with lower progression-free survival and OS. Moreover, more peritoneal recurrences were observed in patients with positive peritoneal cytology. Despite the absence of an association between positive peritoneal cytology and disease recurrence in the present study, a correlation with poor OS was identified. This finding is consistent with the results of previous studies.

The recommended approach for all types of HGEC is LN dissection, due to the high risk of nodal involvement. However, the literature contains some studies that have found no evidence that LN dissection provides any survival benefit. The NCCN recommends para-aortic LN dissection with pelvic LN dissection for all patients diagnosed with HGEC.<sup>[23,26,27]</sup> The potential impact of LN dissection on survival can be attributed to two main factors: Accurate staging and thus planning of appropriate adjuvant therapy, and removal of both metastatic and occult lesions through lymphadenectomy. In a study by Venigalla et al.<sup>[28]</sup> of 7250 patients with EC with serous, clear cell and carcinosarcoma histotypes, multivariate analysis showed a significantly lower HR for death in patients undergoing pelvic LN dissection (HR=0.65, 95% CI: 0.56-0.74) and pelvic + para-aortic LN dissection (HR=0.54, 95% CI: 0.48-0.62) compared to patients without LN dissection.<sup>[28]</sup> In a study by Alagkiozidis et al.<sup>[29]</sup> involving 158 carcinosarcoma and 116 serous carcinoma endometrial cancer patients, lymph node dissection improved survival. In a study by Buldukoglu et al.<sup>[30]</sup> in a cohort of 60 patients diagnosed with HGEC, LN positivity was found to be associated with increased disease recurrence and increased death rate, and LN positivity was found to be an independent prognostic factor for survival. However, in a study conducted by Baquedano et al.<sup>[31]</sup> on 373 patients with HGEC, LN positivity was not found to be an independent prognostic factor associated with survival. In the present study, in accordance with a significant number of studies in the literature, both pelvic and paraaortic LN positivity was found to be a prognostic factor associated with both disease recurrence and OS.

Although tumour size was not found to be associated with overall survival in the present study, in a study by Akış et al.<sup>[32]</sup> involving a total of 146 patients with endometrioid EC, including 27 patients with FIGO stage 3 disease, tumour size was identified as the most important risk factor for LN involvement. In this context, the identification of LN involvement as an important prognostic factor for overall survival and recurrence as defined by the present study highlights the importance of understanding the factors that determine LN involvement.

## Limitations and Strengths

This retrospective study, conducted at a tertiary referral center, is subject to inherent biases, including selection bias and potential incomplete data recording. The modest sample size limited the statistical power to detect subtle associations and perform comprehensive multivariate analyses for all variables. Additionally, the study relied on histological classification rather than molecular profiling (e.g., TCGA-based subtypes: POLE ultramutated, MSI, copy-number low, and copy-number high). This is a significant limitation, as molecular classification can refine risk stratification, predict treatment response, and guide targeted therapies more effectively than histology alone, particularly in HGEC, where tumor heterogeneity is pronounced. The absence of molecular data may have missed subtype-specific prognostic factors, limiting the applicability of findings in settings with routine molecular testing.

Despite these limitations, the study's focus on HGEC, a relatively rare and aggressive subset of EC, is a key strength. Most EC research centers on low-grade endometrioid tumors, where prognostic factors are well-established. By using rigorous statistical methods, this study identifies independent prognostic factors for HGEC, contributing valuable insights to patient management.

## CONCLUSION

The presence of positivity in pelvic LN, para-aortic LN, disease stage and adjuvant therapies were associated with disease recurrence. Multivariate analysis revealed that histotype (DE/undifferentiated) and positive peritoneal cytology were important independent prognostic factors for overall survival. In this context, clinicians' understanding of the factors influencing disease recurrence and overall survival is crucial to inform patient counselling and subsequent management approaches.

### Ethics Committee Approval

The study was approved by the Ethics Committee of Antalya Training and Research Hospital (Date: 13.06.2024, Decision No: 2024-172).

### Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: N.Y., I.U.; Design: N.Y., I.U.; Supervision: N.Y., I.U., T.T.; Fundings: A.A., Mu.G., Me.G.; Materials: A.A., Mu.G., Me.G.; Data collection &/or processing: A.A., Mu.G., Me.G.; Analysis and/or interpretation: N.Y., I.U., T.T.; Literature search: N.Y., I.U.; Writing: N.Y.; Critical review: N.Y., I.U., T.T.

### Conflict of Interest

The authors did not present any potential conflicts of interest.

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## Data availability

Should further information be required, it will be made available upon reasonable request. The raw data were generated at the Antalya Training and Research Hospital, which is affiliated with the Health Science University. The data derived from this study that support the findings presented herein are available from the corresponding author upon request.

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## Yüksek Dereceli Endometriyum Kanserli Hastalarda Hastalık Rekürrensini ve Genel Sağkalımı Etkileyen Faktörler

**Amaç:** Bu çalışmanın temel amacı, yüksek dereceli endometriyum kanserli hastalarda hastalık nüksünü ve genel sağkalımı etkileyen faktörleri belirlemektir.

**Gereç ve Yöntem:** Çalışmaya Ocak 2017 ile Aralık 2021 tarihleri arasında endometriyal kanser tanısı ile primer cerrahi geçiren ve postoperatif patoloji raporlarına göre seröz, berrak hücreli, karsinosarkom, mikst tip, grade 3 endometrioid veya DE/undiferansiyel endometriyal kanser histolojisi tanısı alan kadınlar retrospektif olarak dahil edilmiştir. Veri seti hasta dosyalarından ve elektronik jinekolojik onkoloji kliniği veri tabanından elde edilmiştir.

**Bulgular:** Toplam 81 hasta analize dahil edildi. 26 (%32.1) hastada nüks görülmüştür. Pelvik lenf nodu pozitifliği, para-aortik lenf nodu pozitifliği, hastalık evresi ve adjuvan tedavi hastalık nüksü ile ilişkili bulunmuştur. P değerleri sırasıyla 0.005; 0.009; 0.019; 0.002 ve 0.009 idi. Genel sağkalım süresi 39 aydı. Çok değişkenli analizde sadece histotip (DE/farklılaşmamış, Hazard ratio (HR): 4.028 Güven aralığı (CI): 1.208–13.434; P=0.023) ve pozitif peritoneal sitoloji (HR: 3.719; CI:1.408-9.827; P=0.008) genel sağkalım için anlamlı bağımsız prognostik faktörler olarak saptanmıştır.

**Sonuç:** Yüksek dereceli endometriyal kanserlerde histotip ve pozitif peritoneal sitoloji daha kötü bir genel sağkalım ile ilişkili olabilir.

**Anahtar Sözcükler:** Endometriyal kanser; hastalık rekürrensi; genel sağkalım; peritoneal sitoloji; yüksek dereceli histoloji.

# Genetic Variants Associated with Hypospadias: Insights from the Eastern Anatolia Region

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**Keywords:** Hypospadias; polymorphism; steroid 5-alpha reductase type 2



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## ABSTRACT

**Objective:** This study investigates genetic factors contributing to hypospadias in patients from Eastern Anatolia, aiming to identify pathogenic variants and enhance diagnosis and personalised treatment strategies.

**Methods:** An extensive evaluation was performed on 124 patients diagnosed with hypospadias, incorporating clinical examinations and family history reviews. Next-generation sequencing (NGS) was utilised to evaluate DNA samples, with a focus on 26 genes associated with 46,XY sexual development abnormalities. The genetic variations identified were then categorised according to the standards established by the American College of Medical Genetics (ACMG). This process involved a comparison with 124 healthy individuals who served as a control group.

**Results:** It is notable that the investigation yielded several significant genetic discoveries, comprising probable deleterious mutations in genes such as SRD5A2, MAP3K1, and LHCGR. It is notable that 51 subjects exhibited the homozygous c.265C>G (p.Leu89Val) mutation in the SRD5A2 gene, while 19 patients presented with the heterozygous form. The investigation revealed that neither variant was present in the control group. The variant was thus categorised as a variant of unknown significance (VUS), on the basis of its possible pathogenicity. Furthermore, other VUSs were identified in the SOX9, DYNC2H1, and GATA4 genes.

**Conclusion:** The development of hypospadias is significantly influenced by genetic factors. The present study identified SRD5A2 c.265C>G as a candidate for further functional research, emphasising the significance of genetic analysis in the diagnosis of sexual development abnormalities. Advances in genomic technologies, such as NGS, hold considerable potential in identifying therapeutic targets, thereby enhancing our understanding, diagnosis and treatment of hypospadias.

## INTRODUCTION

Hypospadias is caused by inadequate virilization of the genital tubercle, resulting in the urethral orifice being abnormally positioned from the ventral side of the glans penis to the perineum, often accompanied by ventral curvature (chordee) and abnormal prepuce formation.<sup>[1]</sup> Severe forms, such as penoscrotal hypospadias, are associated with other congenital anomalies and are usually detected between 29 and 34 weeks of gestation, while isolated glanular hypospadias can be diagnosed earlier at 20 weeks.<sup>[2,3]</sup>

Hypospadias is a condition influenced by various genetic and environmental factors, with many genes identified as

critical to its etiology. These genes play vital roles in urogenital development, steroid metabolism, and sex differentiation. Notably, genes such as GLI3, CYP11A1, CYP17A1, EGF, TGFBR3, FGFR2, RYR1, INSL3, ADAT3, ARNT2, SNAP29, CYP17A2, and DGKK have been associated with the condition.<sup>[4]</sup> Genetic mutations in NR5A1, SRD5A2, and AR have been identified as mutational hotspots in severe cases of hypospadias. Studies have shown that genetic causes account for approximately 30% of all cases and 28% of severe cases.<sup>[5]</sup> Moreover, altered methylation statuses of candidate genes like WTI, SFI, BMP4, BMP7, HOXA4, HOXB6, AR, FGF8, FGFR2, HSD3B2, SRD5A2, ATF3, MAMLD1, MID1, BNC2, ESRI, ESR2, DGKK, CYP17A1, GSTM1, GSTT1, CTGF, CYR61, and EGF have been ob-

served in hypospadias patients.<sup>[6]</sup> Specific mutations in SRD5A2, AR, and MID1 have been correlated with abnormal male genital development and hypospadias, with a reported genetic abnormality rate of 22.2% in affected patients.<sup>[7]</sup> Genetic polymorphisms in the RYR1 gene are linked to the severity of the condition, while environmental factors such as pregnancy complications, maternal drug use, and low birth weight have been identified as significant risk contributors.<sup>[8]</sup> Genome-wide association studies (GWAS) have revealed novel risk loci, including the 12q13.13 region, and demonstrated that disruption of SPI and SP7 transcription factor activity is associated with multiple hypospadias-related genes.<sup>[9]</sup> Additionally, severity-specific genetic associations have been noted, with SNPs in STS and STARD3 linked to severe hypospadias and an AR gene SNP associated with Type III hypospadias.<sup>[10]</sup> Furthermore, novel genetic variants in genes like HSD3B2 have been implicated in familial cases of hypospadias.<sup>[11]</sup>

Cases of glandular hypospadias generally have normal karyotypes. However, abnormal karyotypes are more common in severe hypospadias with conditions such as undescended testis.<sup>[12]</sup> This is explained by the fact that chromosomal changes tend to be familial in origin and that de novo cases are more rare.<sup>[13]</sup> Undescended testis in the setting of hypospadias may be a reason for further assessment for intersex. Studies show that about 8% of boys with hypospadias have undescended testicles.<sup>[14]</sup> There is also a known link between hypospadias and undescended testicles, and studies show that these conditions can occur together.<sup>[15]</sup> There was a positive correlation between the severity of hypospadias and the presence of intersex, suggesting that the two conditions may be linked.<sup>[16]</sup> The presence of undescended testes in the context of hypospadias has been associated with other abnormalities such as epididymal abnormalities and testicular tumors.<sup>[17]</sup> Furthermore, between 9% and 16% have been reported to have hypospadias associated with inguinal hernias and/or hydrocele.<sup>[18]</sup>

Hypospadias is often associated with other findings and cryptorchidism. There are at least 49 known syndromes in which hypospadias is associated. The presence of a micropenis, an undescended testis and/or scrotal anomalies in 38 (78%) of these 49 syndromes seems to point to an endocrinopathy in the etiology of hypospadias.<sup>[19]</sup> Hypospadias can be associated with several intersex conditions. These include adrenogenital syndrome, mixed gonadal dysgenesis, male pseudohermaphroditism, and true hermaphroditism. Although hypospadias and intersex represent different points on a spectrum, sexual identity dilemma is rarely seen in boys with an isolated urethral orifice in the shaft of a normal-sized penis, but the likelihood of intersex increases when hypospadias is associated with other signs such as a urethral orifice in the scrotum or perineum. In particular, hypospadias in association with cryptorchidism has the potential to be an indication of intersex conditions. If the undescended testis cannot be palpated, the risk of intersex may be as high as 50%.<sup>[16]</sup>

Steroid 5 $\alpha$ -reductase (SRD5A2) is located on chromosome 2 and is the enzyme that converts testosterone into the more potent hormone dihydrotestosterone.<sup>[20]</sup> SRD5A2 consists of 5 exons and is predominantly expressed in the external genitalia and prostate.<sup>[21]</sup> Mutations in the SRD5A2 gene can lead to malfunctioning of the 5 $\alpha$ -reductase type 2 enzyme, resulting in conditions such as 46,XY disorders of sexual development.<sup>[22]</sup> The SRD5A2 gene has been shown to affect semen quality, and changes in this gene can affect semen quality.<sup>[23]</sup>

## MATERIALS AND METHODS

This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (No: BAEK 2020/23-220, Date: 21/12/2020) and conducted according to the Declaration of Helsinki.

Our patients consisted of 124 people living in the East Anatolian region of Turkey between December 2020 and December 2024. They applied to or consulted Erzurum Regional Hospital with the complaint of hypospadias. All patients were assessed for family history, consanguinity status and clinical findings. This is a retrospective study conducted in the genetic outpatient clinic. According to the results of the SRD5A2 test, a control group of 124 people was subsequently tested.

### Genetic Analysis

Patient samples were analyzed using an NGS panel containing AKRIC2, AMH, AMHR2, AR, ARX, ATRX, CYB5A, CYP11A1, CYP17A1, DHCR7, DHH, DYNC2H1, GATA4, HSD17B3, HS6ST1, HCCS, LHCGR, MAMLD1, MAP3K1, NR5A1, OPHN1, SOX9, SRD5A2, SRY, WT1, ZFPM2 genes (Table 1).

The selection of these genes reflects the genetic diversity and clinical features of 46 XY sex disorders. Blood samples from the patients were used for DNA isolation. DNA isolation was carried out using standard methods. Genetic analysis Genomic DNA was isolated from peripheral blood samples (200  $\mu$ L) using the Qiagen QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The DNA samples obtained were prepared and sequenced for the NGS panel. Sequencing was carried out on the Illumina platform. The raw sequencing data obtained were analyzed after primer and quality checks. Genetic variants were evaluated by comparison with relevant databases and literature. For the specific study of the SRD5A2 gene, genomic DNA was isolated from 200  $\mu$ L peripheral blood samples using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. PCR-amplified DNA sequences were sequenced using the Illumina MiSeq platform (Illumina, Inc., San Diego, CA, USA).

The potential adverse health effects of the genetic variations were analyzed using the ClinVar and HGMD Professional databases. Additionally, we employed tools

**Table 1.** Genes and Their Functions Identified in the 46,XY Panel

GENE	FUNCTION/RELATION
AKR1C2	Involved in testosterone metabolism; mutations can lead to hormonal imbalances.
AMH/AMHR2	Critical for male urogenital development; regulates anti-Müllerian hormone and its receptor.
AR	Essential for androgen effects; mutations increase risk of hypospadias.
ARX and ATRX	Roles in male urogenital and brain development; loss of function can lead to hypospadias and other anomalies.
CYB5A and CYP11A1	Involved in steroidogenesis; mutations linked to hormonal disorders.
CYP17A1	Crucial for testosterone synthesis; deficiencies associated with hypospadias.
DHCR7	Affects steroid metabolism; mutations disrupt urogenital development.
DHH	Associated with testis development and urethral differentiation.
DYNC2H1	Plays a role in cellular transport; linked to urogenital anomalies.
GATA4	Regulates gonadal development and gene expression.
HSD17B3	Critical for testosterone production; mutations affect sexual differentiation.
HCCS	Linked to mitochondrial functions; may indirectly influence hypospadias risk.
LHCGR	Luteinizing hormone receptor; deficiencies reduce testosterone production.
MAMLD1	Commonly associated with hypospadias.
MAP3KI	Involved in signal transduction for sexual differentiation.
NR5A1	Affects gonadal development and steroidogenesis.
OPHN1	Plays a role in cytoskeletal organization and signal transduction.
SOX9	Essential for gonadal development; mutations linked to hypospadias.
SRD5A2	Catalyzes conversion of testosterone to dihydrotestosterone; deficiencies cause hypospadias.
SRY	Key regulator of male sex differentiation.
WT1	Important for urogenital system development.
ZFPM2 (FOG2)	Transcription factor involved in sex differentiation.

such as Revel, AlphaMissense, Eve, MUT Assessor, SIFT, Polyphen2, FATHMM, DANN, MetaLR, PrimateAI, and BayesDel. Variants were deemed pathogenic or possibly pathogenic if they were associated with known pathogenic mechanisms, observed in the patient cohort, rare among controls, involved conserved amino acid changes, and/or predicted to be deleterious. Confirmation of all variants was performed through Sanger sequencing. The SRD5A2 gene analysis of healthy individuals in the control group was performed using an AB 3130 XL 16-capillary Sanger sequencer. The start (forward) primer used in this analysis was “5'-CGGAATTCAACACGGCGCGATGCAGGT TTCA-3'” and the end (reverse) primer was “5'-GGTC TAGAGGATAGGGTCCCTGGAAGGGTAGG-3'”. These primers ensured efficient copying and sequencing of the relevant region of DNA. All variants were confirmed by Sanger sequencing. Patient phenotypes were reviewed with their physicians. Statistical analysis was performed using SPSS 25.0, assessing the prevalence of the polymorphism and its correlation with hypospadias risk factors through tests and logistic regression.

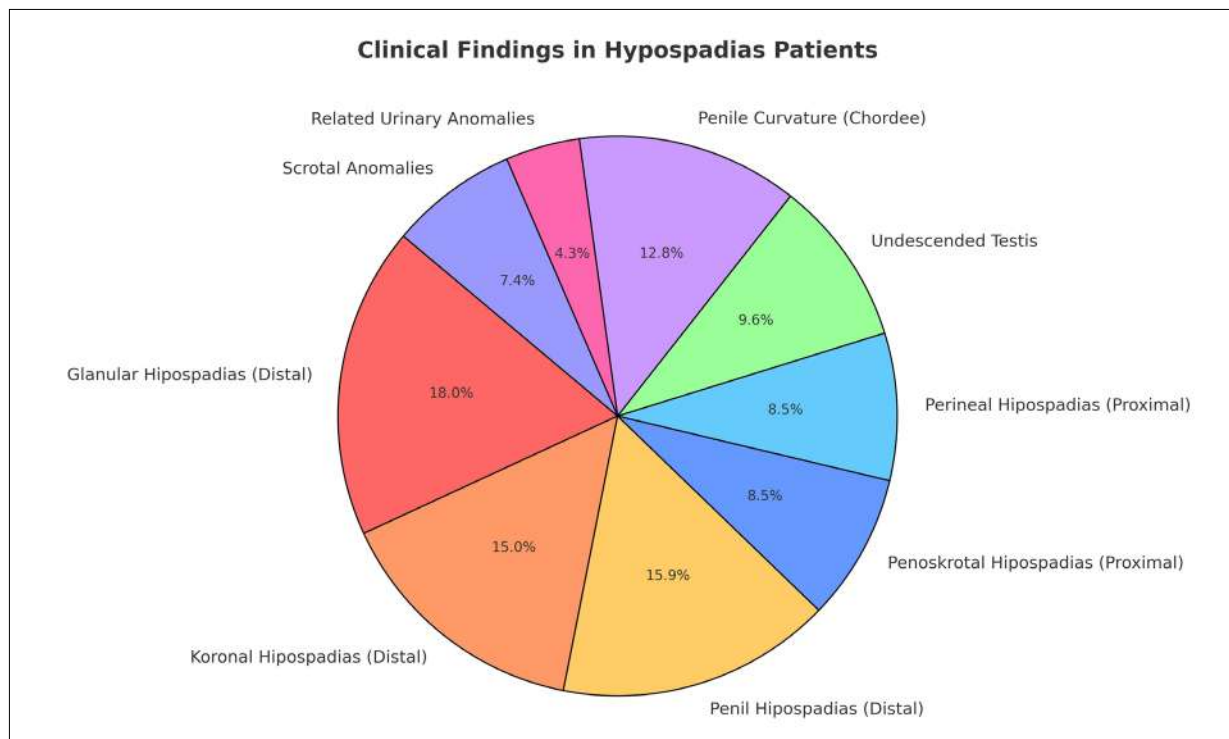
## RESULTS

Among 124 hypospadias patients, almost all of whom were

neonates or 1-month-old infants from the Eastern Anatolian region, 13% (16 patients) had a history of hypospadias in first-degree relatives, and 8% (10 patients) had a distant degree of consanguinity (cousin marriage) between the parents. According to the clinical findings, distal hypospadias (including glanular, coronal, and penile types) was observed in 48.9% (61 patients), whereas proximal hypospadias (including penoscrotal and perineal types) was found in 17% (21 patients). Additionally, 9.6% (12 patients) had undescended testis, 12.8% (16 patients) had penile curvature (chordee), 4.3% (5 patients) had associated urinary anomalies, and 7.4% (9 patients) had scrotal anomalies (Fig. 1). Most patients were diagnosed at birth (77.4%, 96 patients) or within 1 month (22.6%, 28 patients).

The patients were referred to the pediatric urology and pediatric surgery departments and then to the medical genetics outpatient clinic. Firstly, chromosome analysis was performed in all patients, and the chromosome analysis result was 46,XY. Then, the 46,XY Disorders of Sexual Development/Complete Gonadal Dysgenesis NGS panel was analyzed, revealing several significant genetic findings that highlight the complex genetic basis of these conditions.

Among the detected mutations, the variants in LHCGR



**Figure 1.** Clinical findings in hypospadias patients.

**Table 2.** Results of the NGS panel test

GENE	HYOSPADIAS TYPE	INHERITANCE TYPE	LOCATION	CLINICAL IMPORTANCE (ACCORDING TO ACMG CRITERIA)
LHCGR:c.1331T>G p.Phe444Cys	Proximal (Penosrotal)	Heterozygous	A.D.	L.PATHOGENIC
MAP3K1:c.602G>A p.Trp201*	Proximal (Perineal)	Heterozygous	A.D.	L.PATHOGENIC
SRD5A2:c.589G>A p.Glu197Lys	Proximal (Penosrotal)	Heterozygous	A.R.	L.PATHOGENIC
GATA4:c.1000+56 C>A	Distal (Coronal)	Homozygous	A.D.	VUS
DYNC2H1:c.3181C>G p.Leu1061Val	Distal (Penile)	Heterozygous	A.D., A.R.	VUS
DYNC2H1: c.11308 G>A p.Ala3763Thr	Distal (Penile)	Heterozygous	A.D., A.R.	VUS
SOX9:c.200A>G p.Asp67Gly	Distal (Coronal)	Heterozygous	A.D.	VUS
HS6ST1:c.226G>C p.Glu76Gln	Distal (Glanular)	Heterozygous	A.D.	VUS
AMHR2:c.71G>A p.Cys24Tyr	Proximal (Penosrotal)	Heterozygous	A.R.	VUS
AR:c.2450T>C p.Ile817Thr	Proximal (Perineal)	Hemizygous	X.L.R.	VUS
ARX:c.82_84del p.Cys28del	Proximal (Perineal)	Hemizygous	X.L.R.	VUS
ATRX:c.7462C>T p.Gln2488*	Proximal (Penosrotal)	Hemizygous	X.L.R.	VUS
CYP11A1:c.1236+5G>A	Proximal (Penosrotal)	Heterozygous	A.R or A.R	VUS
DHCR7:c.1249G>A p.Ala417Thr	Distal (Penile)	Heterozygous	A.R.	VUS
DYNC2H1:c.12007G>A p.Ala4003Thr	Distal (Penile)	Heterozygous	A.D., A.R.	VUS
GATA4:c.825C>T p.Cys275=	Distal (Coronal)	Heterozygous	A.D.	VUS
MAMLD1:c.602G>A p.Gly201Glu	Distal (Penile)	Hemizygous	X.L.R.	VUS
MAMLD1:c.1234A>T p.Ser412Cys	Distal (Penile)	Hemizygous	X.L.R.	VUS
NR5A1:c.987G>T p.Gln329His	Proximal (Penosrotal)	Heterozygous	A.D.	VUS
SOX9:c.1065_1082del p.Pro359_Ala364del	Distal (Coronal)	Heterozygous	A.D.	VUS
SOX9:c.1330G>A p.Asp444Asn	Distal (Coronal)	Heterozygous	A.D.	VUS
WT1:c.859G>A p.Ala287Thr	Proximal (Penosrotal)	Heterozygous	A.D.	VUS
ZFPM2:c.617T>C p.Leu206Pro	Proximal (Perineal)	Heterozygous	A.D.	VUS

**Table 3.** Results for SRD5A2 gene

GENE	INHERITANCE TYPE	CLINICAL IMPORTANCE (ACCORDING TO ACMG CRITERIA)	NUMBER OF RESULTS
SRD5A2 c.265C>G p.Leu89Val	Homozygous	VUS	51
SRD5A2 c.265C>G p.Leu89Val	Heterozygous	VUS	19
SRD5A2 c.265C>T	Heterozygous	VUS	2
Normal			52

(c.1331T>G, p.Phe444Cys), MAP3K1 (c.602G>A, p.Trp201\*), and SRD5A2 (c.589G>A, p.Glu197Lys) were classified as likely pathogenic and were predominantly associated with proximal (penoscrotal) hypospadias, suggesting a strong genetic contribution to these phenotypes. In addition, numerous variants of uncertain significance (VUS) were identified in a wide range of genes, including GATA4 (c.1000+56 C>A), DYNC2H1 (c.3181C>G, p.Leu1061Val; c.11308 G>A, p.Ala3763Thr), and SOX9 (c.200A>G, p.Asp67Gly), among others. These VUS mutations were more frequently observed in distal hypospadias subtypes, including coronal, penile, and glanular presentations, emphasizing the need for further functional and clinical studies to determine their pathogenic roles. Of particular note, hemizygous variants in AR (c.2450T>C, p.Ile817Thr), ARX (c.82\_84del, p.Cys28del), and ATRX (c.7462C>T, p.Gln2488\*) suggest a possible X-linked contribution to the etiology of these disorders\*. These X-linked variants were primarily found in proximal hypospadias cases (penoscrotal or perineal subtypes), indicating a possible role of androgen receptor signaling in the etiology of these phenotypes. The recurrence of VUS in genes such as SOX9 and MAMLD1 suggests their potential relevance in the phenotypic spectrum of these disorders, particularly in distal hypospadias phenotypes. These findings further underscore the genetic heterogeneity and complexity of 46,XY DSD-associated hypospadias (Table 2).

However, the SRD5A2 homozygous c.265C>G p.Leu89Val variant (classified as a VUS) was identified in 51 patients, while the heterozygous form was detected in 19 patients. Considering that the c.265C>G p.Leu89Val variant may not be a VUS but may be potentially pathogenic, the SRD5A2 gene was analysed in a control group of 124 individuals. No homozygous or heterozygous forms of the c.265C>G p.Leu89Val variant were detected in this control group (Table 3).

## DISCUSSION

The results of this study highlight the importance of genetic factors in 46,XY disorders of sex development and hypospadias. Variants in the GATA4, DYNC2H1 and SOX9 genes support the critical role of these genes in sex development and gonadal differentiation. In particular, VUS variants identified in the GATA4 and SOX9 genes further emphasize the role of these genes in regulating important

pathways in sex development, while the presence of variants in the DYNC2H1 gene indicates their potential impact on sex development.<sup>[24]</sup>

Studies have shown that the rate of genetic diagnosis in 46,XY DSD patients is approximately 43%, suggesting that a significant proportion of cases remain undiagnosed at the genetic level.<sup>[24]</sup> Despite advances in understanding the genetic basis of sex determination, most cases of 46,XY gonadal dysgenesis remain without a definitive genetic diagnosis.<sup>[25]</sup> In addition, studies have shown whether GATA4 variants are associated with heart defects in people with 46,XY DSD in the context of additional knock-outs in other DSD genes.<sup>[26]</sup>

SOX9 is essential for male sex development. This is particularly evident in conditions such as 46,XY DSD, where patients show sex reversal when SOX9 is lost.<sup>[27]</sup> In addition, DYNC2H1 variants have been linked to limb development abnormalities such as polydactyly, highlighting its role in skeletal development.<sup>[28]</sup> The importance of these genes in the complex processes of sex determination and gonadal development in humans is highlighted by the combination of genetic findings in these genes. In this case, interaction of genetic variants in GATA4, DYNC2H1 and SOX9 sheds light on the complex mechanisms of sex development and gonadal differentiation in individuals with 46,XY DSD and related conditions. These genes play a critical role in controlling key pathways for proper sex development. Variations in these genes can have profound effects on the phenotypic outcomes observed in affected individuals.

The SRD5A2-V89L polymorphism shows a significant association in studies of hypospadias patients in different populations, based on the findings in the literature.<sup>[29-31]</sup> In addition, SRD5A2-V89L and SRD5A2-A49T polymorphisms have been shown to be associated with hypospadias in a study of the Iranian population.<sup>[32]</sup> The V89L polymorphism in the SRD5A2 gene has been extensively studied in prostate cancer in different populations and the results have been conflicting.<sup>[33,34]</sup> The presence of a leucine (L89) at codon 89 has been shown to cause a 30% reduction in the activity of the enzyme, resulting in lower levels of testosterone metabolites.<sup>[35,36]</sup> The difference in the functional potential of these two gene products makes this polymorphism of particular interest in the pathogenesis of hypospadias. In another study, the V89 allele of the SRD5A2 gene, when homozygous, was reported to reduce the risk of hypospadias in Turkish patients with a

higher leucine frequency than in Swedish patients.<sup>[30]</sup>

The analysis revealed a remarkable prevalence of the c.265C>G (p.Leu89Val) variant in the SRD5A2 gene in patients, with 51 homozygous and 19 heterozygous cases identified. Although currently classified as a variant of uncertain significance (VUS), its potential pathogenicity is suggested. To investigate further, the SRD5A2 gene was analysed in a control group of 124 individuals in whom the variant was absent. These results suggest that the c.265C>G (p.Leu89Val) variant is more common in hypospadias patients and may contribute to the development of the disease. However, further studies and functional analysis are needed to confirm its pathogenic role.

Given these findings, the importance of genetic analysis in diagnosing and treating sexual development disorders such as hypospadias becomes even more apparent. In identifying genetic variants that may provide potential pathogenic and therapeutic targets, the use of advanced technologies such as NGS plays an important role. In addition, a better understanding of the pathogenicity and clinical significance of specific mutations in the SRD5A2 gene may be achieved by further investigation of their association with hypospadias risk.

## CONCLUSION

This study highlights the potential importance of genetic analysis in understanding the genetic basis of hypospadias and similar disorders of sexual development and in the management of these conditions. The functional impact of these genetic variants and potential therapeutic targets on the development of hypospadias should be further clarified in future studies.

### Ethics Committee Approval

The study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (Date: 21.12.2020, Decision No: BAEK 2020/23-220).

### Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: O.Y., M.D., H.D., M.C.G.; Design: O.Y., M.D., H.D., M.C.G.; Supervision: O.Y.; Fundings: M.D., H.D.; Materials: O.Y., M.D., H.D., M.C.G.; Data collection &/or processing: M.C.G.; Analysis and/or interpretation: O.Y.; Literature search: M.C.G.; Writing: O.Y.; Critical review: O.Y., M.D., H.D., M.C.G.

### Conflict of Interest

The authors have no conflicts of interest to declare.

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## Hipospadias ile İlişkili Genetik Varyantlar: Doğu Anadolu Bölgesi'ne İlişkin Bulgular

**Amaç:** Bu çalışma, Doğu Anadolu'daki hastalarda hipospadias katkıda bulunan genetik faktörleri araştırmakta, patojenik varyantları tanımlamayı ve tanı ve kişiselleştirilmiş tedavi stratejilerini geliştirmeyi amaçlamaktadır.


**Gereç ve Yöntem:** Hipospadias tanısı konulan 124 hasta üzerinde klinik muayene ve aile öyküsü incelemelerini içeren kapsamlı bir değerlendirme yapılmıştır. DNA örneklerini değerlendirmek için yeni nesil dizileme (NGS) kullanılmış ve 46,XY cinsel gelişim anormallikleri ile ilişkili 26 gene odaklanılmıştır. Tanımlanan genetik varyasyonlar daha sonra American College of Medical Genetics (ACMG) tarafından belirlenen standartlara göre kategorize edilmiştir. Bu süreç, kontrol grubu olarak görev yapan 124 sağlıklı bireyle bir karşılaştırmayı içeriyordu.

**Bulgular:** Araştırmanın SRD5A2, MAP3K1 ve LHCGR gibi genlerde olası zararlı mutasyonları içeren birkaç önemli genetik keşif ortaya çıkarması dikkate değerdir. SRD5A2 geninde homozigot c.265C>G (p.Leu89Val) mutasyonu 51 kişide görülürken, 19 hastada heterozigot formun görülmesi dikkat çekicidir. Araştırma, kontrol grubunda her iki varyantın da bulunmadığını ortaya koymuştur. Bu nedenle varyant, olası patojenitesi temelinde önemi bilinmeyen varyant (VUS) olarak kategorize edilmiştir. Ayrıca, SOX9, DYNC2H1 ve GATA4 genlerinde başka VUS'lar da tespit edilmiştir.

**Sonuç:** Hipospadias gelişimi genetik faktörlerden önemli ölçüde etkilenmektedir. Bu çalışma, SRD5A2 c.265C>G'yi daha ileri fonksiyonel araştırmalar için bir aday olarak tanımlamış ve cinsel gelişim anormalliklerinin tanısında genetik analizin önemini vurgulamıştır. NGS gibi genomik teknolojilerdeki gelişmeler, terapötik hedeflerin belirlenmesinde önemli bir potansiyele sahiptir, böylece hipospadias anlayışımızı, teşhisimizi ve tedavimizi geliştirir.

**Anahtar Sözcükler:** Hipospadiyas; polimorfizm; steroid 5-alfa redüktaz tip 2.

# A Comparative Analysis of Three Fixation Techniques for Non-Articular Pediatric Distal Tibia Fractures

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**Keywords:** Fracture fixation; pediatric;tibia; weight-bearing.



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## ABSTRACT

**Objective:** To evaluate the relationship between the distance of pediatric distal tibial fractures to the physis and the fixation methods used, as well as their impact on weight-bearing times and complications.

**Methods:** This retrospective study included patients with open physes who underwent surgical treatment for pediatric distal tibial metaphyseal fractures in two centers between 2019 and 2024. Patients were grouped based on the fixation method used: K-wire, titanium elastic nails (TEN), or plate-screw fixation. Data collected included patient demographics, fracture distance to the physis, the ratio of fracture distance to metaphyseal width (DP/MW), weight-bearing times, and complications such as infection and reduction loss. Statistical analyses were performed using non-parametric tests, with a significance threshold of  $p < 0.05$ .

**Results:** The study included 75 patients (52 males, 23 females) with a mean age of 9.7 years. Fixation methods included K-wire fixation (27 patients), TEN fixation (26 patients), and plate-screw fixation (22 patients). Pain-free weight-bearing was observed after a median of 8 weeks [7-9] in the K-wire fixation group, a median of 6 weeks [6-7] in the plate-screw fixation group, and a median of 6 weeks [5-6] in the TEN fixation group. The duration of pain-free weight-bearing was significantly longer in the K-wire group. A positive correlation was observed between the fracture's distance to the physis and earlier weight-bearing ( $p = 0.041$ ). Superficial infection developed in three patients (11.11%) who were fixed with K-wires and in one patient (4.55%) in the plate-screw fixation group. While loss of reduction was reported in one patient (3.70%) in the K-wire fixation group, no loss of reduction was observed in the other groups. No statistically significant differences in complications were observed between the groups.

**Conclusion:** The time to weight-bearing is longer in patients treated with K-wire fixation compared to TEN and plate-screw fixation. Additionally, fractures located farther from the physis allow for earlier weight-bearing. These findings underscore the critical role of fracture location and fixation method in informing treatment strategies. Further randomized controlled trials are essential to validate and strengthen these results.

## INTRODUCTION

Tibia fractures are the third most common fractures of long bones in children.<sup>[1]</sup> Approximately 50–70% of pediatric tibial fractures occur in the distal third of the tibia, while 19–39% occur in the middle third of the tibia.<sup>[2,3]</sup> Although they are usually treated with closed reduction and casting, 100% translation, 1 cm shortening and coronal or sagittal deformity of up to 10° can be tolerated in children under 8 years of age, while 50% translation, 1 cm shortening and 5° coronal or sagittal deformity can only

be tolerated in patients over 8 years of age.<sup>[4,5]</sup> In addition, surgical treatment should be considered in certain special cases (complex fractures with multi-trauma, soft tissue loss, vascular or nerve injuries).<sup>[6]</sup>

The type of fracture, the condition of the soft tissues, the degree of displacement of the fracture, the condition of the fibula and the weight of the child influence the treatment to be applied.<sup>[7,8]</sup> In addition, pediatric distal tibial metaphyseal fractures can often present as oblique, comminuted or transverse fractures.<sup>[9,10]</sup> Fixation methods

such as K-wire, plate screw, external fixator or titanium elastic nail (TEN) fixation are available for the fixation of fractures in this region.<sup>[3,6,11]</sup>

In the management of tibial shaft fractures, fixation using titanium elastic nails (TEN) may be considered even in children weighing more than 50 kg.<sup>[8,12]</sup> However, challenges can arise with TEN fixation due to the expansion of the medullary canal as it approaches the metaphyseal region. Although various fixation techniques have been described, the optimal treatment for pediatric distal tibial diaphyseal-metaphyseal junction fractures remains unclear in the current literature.

In this study, we evaluated distance from the midpoint of the fracture line to the physis, distance of fracture midline to physis/metaphysis width (DP/MW), weight-bearing times, and complications, including infection and loss of reduction, observed during the follow-up of patients treated with K-wires, TEN, and plate-screw fixation for fractures in this region.

## MATERIALS AND METHODS

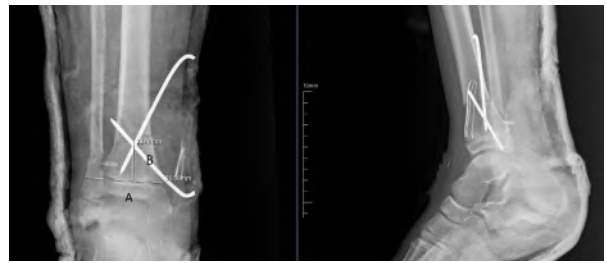
### Ethics Committee Approval

The study was approved by the Ankara Etlik City Hospital Ethics Committee (Date: 10/07/2024, Decision No: AESH-BADEK-2024-457). Two different centers were included in our study: Ankara Etlik City Hospital between November 2022- March 2024 and Ankara Bilkent City Hospital Orthopedics and Traumatology Clinic between March 2019-March 2024.

This study included patients with open physes who underwent surgical treatment for pediatric distal tibial metaphyseal fractures not involving the physis. Eligibility criteria required patients to have a minimum of six months of postoperative follow-up and complete preoperative and postoperative radiological and clinical data. Exclusion criteria encompassed fractures extending to the physis, open fractures, pathological fractures, fractures involving multiple extremities, and cases managed conservatively with casting.

The fracture was defined as a distal metaphyseal fracture according to the Arbeitsgemeinschaft für Osteosynthesfragen (AO) - Pediatric Comprehensive Classification of Long Bone Fractures (PCCF) classification system.<sup>[13]</sup>

Data were collected on patient demographics, including gender, age at the time of fracture, weight and the affected side. Additional variables included the distance from the midpoint of the fracture line to the physis, the ratio of the fracture midline-to-physis distance to the metaphyseal width (DP/MW) (Fig. 1), the fixation method used, and the presence of an associated fibular fracture. The measurements were made by single surgeons and the choice of fixation method is surgical preference. For all patients with displaced fibular fractures, intramedullary K-wire fixation was performed. Follow-up assessments recorded the time to weight-bearing, loss of reduction, the necessity for re-



**Figure 1.** Distal tibia fracture fixed with K-wire, (a) metaphyseal width, (b) the distance from the midpoint of the fracture line to the physis.



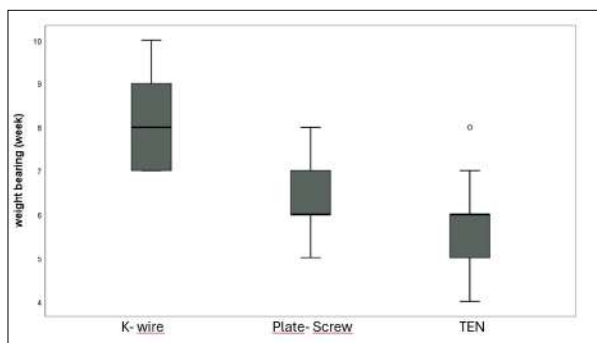
**Figure 2.** Distal tibia fracture fixed with TEN, (a) Preoperative anteroposterior radiograph, (b) Preoperative lateral radiograph, (c) Postoperative anteroposterior radiograph, (d) Postoperative lateral radiograph.

operation, and the presence of infection. After union was seen on the radiograph, the patients were asked to bear weight. The periods mentioned in the study are the weeks during which the patients were able to bear weight without pain. Loss of reduction was defined as an angulation exceeding 5 degrees or a shortening greater than 1 cm.<sup>[14]</sup>

Postoperative protocols were tailored according to the treatment method employed. In the K-wire fixation group, a short leg splint was applied for one month postoperatively, whereas the TEN fixation group utilized a splint for two weeks (Fig. 2). No splinting was required for patients in the plate and screw fixation group (Fig. 3). All patients were allowed partial weight-bearing after the first postoperative month. All patients received cefazolin as preoperative prophylaxis, followed by three additional doses within the first 24 hours postoperatively. Routine follow-up evaluations were conducted at the second, fourth, sixth, seventh, and eighth weeks. Weight-bearing was permitted



**Figure 3.** Distal tibia fracture fixed with TEN, (a) Preoperative anteroposterior radiograph, (b) Preoperative lateral radiograph, (c) Postoperative anteroposterior radiograph, (d) Postoperative lateral radiograph.



**Figure 4.** Weight-bearing timelines based on fixation types, TEN, titanium elastik nail.

once callus formation was observed in three planes on radiographs. K-wires were removed following radiographic confirmation of union. In contrast, no standardized timeline was established for the removal of TEN or plate implants. Instead, implant removal for these groups was planned collaboratively with the patient after achieving radiographic union, with a second procedure scheduled at an appropriate time.

### Statistical analysis

The calculation and statistical analysis of the study data were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). The normality of the distribution for continuous variables was assessed using the Kolmogorov-Smirnov test, which revealed that none of the continuous variables followed a normal distribution. Consequently, continuous variables were summarized using median, min-

imum, and maximum values. Categorical variables were presented as frequencies (n) and percentages (%). For comparisons of continuous variables between groups, the Kruskal-Wallis test and Mann-Whitney U test were applied for non-normally distributed data. The relationship between two continuous variables was evaluated using Spearman's rho correlation coefficient. A p-value of <0.05 was considered statistically significant.

## RESULTS

A total of 75 patients, comprising 52 males (69.3%) and 23 females (30.6%), were included in the study. Of these patients, 42 (56%) underwent surgery on the right distal tibia, while 33 (44%) were treated on the left side. Fixation methods included K-wire fixation in 27 patients (36%), TEN fixation in 26 patients (34.6%), and plate-screw fixation in 22 patients (29.3%) (Table 1). No significant differences were observed between the groups in terms of age or weight.

Reduction loss was observed in one patient (3.7%) treated with K-wire fixation, necessitating conversion to plate-screw fixation. Distal fibular fractures accompanying distal tibial fractures were present in 4 patients (14.8%) in the K-wire group, 5 patients (22.7%) in the plate-screw group, and 5 patients (19.2%) in the TEN group. Superficial infections occurred in 3 patients treated with K-wire fixation and 1 patient treated with plate-screw fixation, all of which were successfully managed with oral antibiotic therapy. Due to the limited number of cases with reduction loss, concomitant fibular fractures, and superficial infections, a statistically reliable evaluation could not be performed (Table 1).

No significant differences were observed between the three groups in terms of the distance from the fracture midline to the physis ( $p=0.474$ ) and the ratio of the fracture midline-to-physis distance to the metaphyseal width ( $p=0.615$ ). Pain-free weight-bearing was observed after a median of 8 weeks [7-9] in the K-wire fixation group, a median of 6 weeks [6-7] in the plate-screw fixation group, and a median of 6 weeks [5-6] in the TEN fixation group. Pairwise post-hoc comparisons revealed significantly longer weight-bearing times in the K-wire group compared with both the TEN group ( $p=6.0 \times 10^{-9}$ ) and the plate-screw group ( $p=1.44 \times 10^{-6}$ ). The duration of pain-free weight-bearing was significantly longer in the K-wire group (Table 2).

Analyzing the relationship between the distance to the physis and the union and weight-bearing times, it was found that as the distance from the physis increased, weight-bearing could be initiated earlier. ( $p=0.041$ )

## DISCUSSION

The most significant finding of our study is that the time to weight-bearing was longer in patients treated with K-wire fixation, while fractures located farther from the ph-

**Table 1.** Demographic data and informative data about surgery

	K -Wire		Plate and Screw		Titanium Elastic Nail	
	n	%	n	%	n	%
Gender						
Male	21	77.78	13	59.09	18	69.23
Female	6	22.22	9	40.91	8	30.77
Side						
Left	16	59.26	6	27.27	11	42.31
Right	11	40.74	16	72.73	15	57.69
Loss of Reduction						
No	26	96.30	22	100.00	26	100.00
Yes	1	3.70	0	0.00	0	0.00
Fibula Fracture						
No	23	85.19	17	77.27	21	80.77
Yes	4	14.81	5	22.73	5	19.23
Infection						
No	24	88.89	21	95.45	26	100.00
Superficial	3	11.11	1	4.55	0	0.00

**Table 2.** Relationship between fixation methods and variables

	K-Wire	Plate and Screw	Titanium Elastic Nail	p
Age	12 [10–14]	12 [11–14]	12 [10–13]	0.750
Distance of fracture midline to physis (cm)	2.40 [2.15–2.65]	2.50 [1.93–3.08]	2.45 [2.23–2.60]	0.474
Distance of fracture midline to physis/metaphysis width (DP/MW)	0.43 [0.35–0.50]	0.36 [0.31–0.55]	0.44 [0.33–0.55]	0.615
Weight (kg)	27 [20–36]	28 [18–40]	27 [18–42]	0.612
Weight bearing time (week)	8.0 [7–9]	6.0 [6–7]	6.0 [5–6]	0.000*

\*:Kruskal Wallis test,  $p < 0.05$ .

ysis allowed for earlier weight-bearing. Although the small number of cases with reduction loss precludes statistically significant conclusions, we believe it is crucial to ensure the stability of fixation in patients undergoing K-wire fixation to minimize the risk of reduction loss.

Due to the high remodeling potential in pediatric tibial fractures, conservative treatment plays a significant role. Surgical intervention is planned when acceptable limits are not achieved.<sup>[4]</sup> In tibial shaft fractures, fixation with titanium elastic nails (TEN) is generally considered the appropriate surgical method for children. Depending on the child's weight and age, plate and screws may occasionally be used for fixation. However, as the fracture approaches the metaphyseal region, the widening of the medullary canal can make achieving and maintaining reduction with TEN more challenging.<sup>[15]</sup> In fact, some studies have suggested the potential use of additional K-wire fixation or external fixators in combination to enhance fixation in fractures in this area.<sup>[16,17]</sup> In a study by Heinrich et al.<sup>[18]</sup> on distal tibial shaft fractures, no significant difference in the time

to weight-bearing was found between patients treated with TEN and those treated with plate-screw fixation.<sup>[18]</sup> Masquijo's study reported union times between 8 and 10 weeks for fractures fixed with minimally invasive plates.<sup>[11]</sup> Shen et al.<sup>[15]</sup> noted that most of their patients with distal tibial fractures treated with TEN achieved union at an average of 9.6 weeks. While our findings align with the literature, to the best of our knowledge, no studies have compared K-wire fixation in this context. It is hypothesized that the delayed weight-bearing observed with K-wire fixation may be related to greater micro-movement at the fracture site compared to the other two fixation methods.

In approximately 30% of distal tibial fractures, an associated ipsilateral fibular fracture is observed.<sup>[17]</sup> The presence of a displaced fibular fracture can complicate closed reduction. Moreover, in cases where the fibular fracture is not fixed, there is an increased risk of valgus deformity.<sup>[17]</sup> In distal tibial fractures where tibial fixation is challenging, attention should be paid to the fibular fracture to prevent

shortening and deformity of the fibula. In our study, similar rates of fibular fractures were observed across the groups. Furthermore, the low number of patients with fibular fractures in our cohort and the use of intramedullary fixation with K-wires in all cases might explain the absence of deformity in our results.

In patients treated with K-wire fixation, the removal of the K-wires in an outpatient setting provides a distinct advantage over other patient groups, where implant removal typically requires a second surgical procedure. However, the risk of pin-site infections is higher in the K-wire group, and these patients often require longer follow-up with a short-leg splint. The delayed weight-bearing observed in the K-wire group may be attributed to this prolonged immobilization. In the group treated with titanium elastic nails (TEN), Shen et al.<sup>[15]</sup> reported no cases of infection or skin irritation. However, in a study by Sankar et al.,<sup>[19]</sup> 26% of patients reported pain at the TEN entry site.<sup>[19]</sup> We believe that bending and cutting the elastic nail as close as possible to the cortex at the entry site may prevent patient complaints associated with the procedure.

There were different splinting durations for the three fixation methods used in this study. Because the stability provided by each fixation technique differs, various splinting approaches were applied, and the literature also remains inconclusive on this issue.<sup>[6,20]</sup> Plate and screw fixation provides stable fixation, and follow-up with splinting has been reported to be unnecessary.<sup>[11]</sup> The splinting protocols used in our study are consistent with those reported in the literature, and the timing of partial weight-bearing was similar among the groups. However, it is thought that differences in the duration of immobilization may have influenced the time to achieve pain-free full weight-bearing.

This study has several limitations. The retrospective design and the relatively small sample size are notable constraints. The lack of information regarding the thickness of the K-wires used in the patients represents another limitation. Different splinting protocols differed among groups, which may have confounded the results regarding weight-bearing times. Additionally, the small number of complications precluded robust statistical evaluation. However, conducting the study in two separate centers, including three separate groups, and evaluating the fixation methods according to their distance from the physis could make a significant contribution to the literature. Nevertheless, randomized controlled trials are required to achieve more accurate and robust conclusions.

## CONCLUSION

The most significant findings of our study are that the time to weight-bearing is longer in the K-wire fixation group compared to the TEN and plate-screw groups, and that earlier weight-bearing is possible as the fracture's distance from the physis increases.

### Ethics Committee Approval

The study was approved by the Ankara Etlik City Hospital

Ethics Committee (Date: 10.07.2024, Decision No: AEŞH-BADEK-2024-457).

### Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: Y.E., S.G.; Design: Y.E., S.G., A.S.N.; Supervision: Y.E., H.A.; Fundings: K.S., S.G.; Materials: K.S.; Data collection &/or processing: A.S.N., K.S., H.A.; Analysis and/or interpretation: Y.E., H.A.; Literature search: K.S., S.G.; Writing: Y.E., H.A.; Critical review: Y.E., S.G., A.S.N., K.S., H.A.

### Conflict of Interest

None declared.

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## Non-Artiküler Pediatrik Distal Tibia Kırıkları için Üç Fiksasyon Tekniğinin Karşılaştırmalı Analizi

**Amaç:** Pediatrik distal tibia kırıklarının fizise uzaklığı ile kullanılan fiksasyon yöntemleri arasındaki ilişkiyi ve bunların ağırlık verme süreleri ve komplikasyonlar üzerindeki etkisini değerlendirmek.


**Gereç ve Yöntem:** Bu retrospektif çalışmada, 2019-2024 yılları arasında iki farklı merkezde pediatrik distal tibia metafiz kırıkları nedeniyle cerrahi tedavi uygulanan açık fizisli hastalar incelendi. Hastalar kullanılan fiksasyon yöntemine göre K-teli, titanyum elastik çivi (TEN) veya plak-vida fiksasyonu olmak üzere gruplara ayrıldı. Toplanan veriler arasında hasta demografisi, kırığın fizise uzaklığı, kırık-fizis mesafesinin metafiz genişliğine oranı (DP/MW), ağırlık verme süreleri ve enfeksiyon ile redüksiyon kaybı gibi komplikasyonlar yer aldı. İstatistiksel analizler parametrik olmayan testler kullanılarak yapıldı ve anlamlılık sınırı  $p < 0.05$  olarak belirlendi.

**Bulgular:** Çalışmaya yaş ortalaması 9.7 yıl olan 75 hasta (52 erkek, 23 kadın) dahil edildi. Fiksasyon yöntemleri K-teli ile fiksasyon (27 hasta), TEN fiksasyonu (26 hasta) ve plak-vida fiksasyonu (22 hasta) olarak belirlendi. Ağırlık verme, K-teli grubunda ortalama 8. haftada başlatıldı ve bu süre TEN ve plak-vida gruplarına kıyasla anlamlı derecede uzundu (ortalama 6 hafta,  $p < 0.05$ ). Kırığın fizise uzaklığı ile daha erken ağırlık verme arasında pozitif bir korelasyon gözlemlendi ( $p = 0.041$ ). Yüzeysel enfeksiyonlar 4 hastada görülürken, 1 hastada redüksiyon kaybı rapor edildi. Gruplar arasında komplikasyonlar açısından istatistiksel olarak anlamlı bir fark bulunamadı.

**Sonuç:** K-teli ile fiksasyon yapılan hastalarda ağırlık verme süresi, TEN ve plak-vida fiksasyonu yapılan hastalara göre daha uzun bulundu. Ayrıca, fizisten daha uzak konumlanan kırıklar daha erken ağırlık vermeye olanak sağlamaktadır. Bu bulgular, kırık lokalizasyonunun ve fiksasyon yönteminin tedavi stratejilerinin belirlenmesindeki kritik rolünü vurgulamaktadır. Bu sonuçların doğrulanması ve güçlendirilmesi için daha fazla randomize kontrollü çalışmaya ihtiyaç vardır.

**Anahtar Sözcükler:** Ağırlık verme; kırık fiksasyonu; pediatrik; tibia.

# The Relationship Between BMI, Postoperative Pain Outcomes, and Patient Satisfaction in Patients Undergoing Infraclavicular Brachial Plexus Block

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**Keywords:** Body mass index; infraclavicular brachial plexus block; postoperative pain; regional anesthesia.



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## ABSTRACT

**Objective:** Obesity may influence postoperative pain and patient-reported outcomes after regional anesthesia through mechanisms beyond technical block success. This study evaluated the association between body mass index (BMI) categories and perioperative outcomes following ultrasound-guided infraclavicular brachial plexus block for upper extremity surgery.

**Methods:** This retrospective observational cohort included 83 adult patients ( $\geq 18$  years) undergoing hand, forearm, or elbow surgery with ultrasound-guided infraclavicular brachial plexus block as the primary anesthetic technique. Patients were stratified by BMI as  $<25$  kg/m<sup>2</sup> (n=19), 25–30 kg/m<sup>2</sup> (n=46), and  $\geq 30$  kg/m<sup>2</sup> (n=18). Postoperative pain intensity was assessed using the Visual Analog Scale (VAS; 0–10) at 0, 6, 12, and 24 hours. Secondary outcomes included rescue analgesia, opioid consumption, and patient-reported outcome measures (PROMs), including satisfaction at 1 week and 1 month and subsequent preference for regional anesthesia at 1 month.

**Results:** Demographic characteristics were similar across BMI groups ( $p>0.05$ ). Postoperative VAS scores differed by BMI at 0, 12, and 24 hours, with higher pain levels observed in the BMI  $\geq 30$  group, most pronounced at 24 hours ( $3.11 \pm 1.89$ ), while 6-hour scores were comparable between groups. Rescue analgesic use and opioid consumption did not differ between groups. Patient satisfaction and 1-month subsequent preference for regional anesthesia were significantly lower in the BMI  $\geq 30$  group compared with BMI  $<25$  and BMI 25–30 ( $p<0.001$ ).

**Conclusion:** Higher BMI was associated with worse postoperative pain trajectories and lower patient-reported satisfaction after ultrasound-guided infraclavicular brachial plexus block, despite similar rescue analgesic use and opioid consumption across BMI categories. These findings suggest that BMI stratification may be relevant for individualized perioperative analgesic planning and patient-centered outcome optimization.

## INTRODUCTION

Perioperative anesthetic management increasingly prioritizes strategies that optimize analgesic efficacy while minimizing systemic adverse effects and resource utilization. In upper extremity surgery, ultrasound-guided regional anesthesia techniques, particularly peripheral nerve blocks, play a central role in optimizing intraoperative stability, postoperative recovery trajectories, and patient-reported outcomes by enabling targeted neural blockade with consistent analgesic efficacy and procedural efficiency across diverse patient population.<sup>[1]</sup> Evidence to date indicates

that ultrasound-guided regional anesthesia techniques improve perioperative safety by reducing opioid-related complications and supporting more stable respiratory and hemodynamic profiles, in line with modern perioperative care strategies.<sup>[2]</sup> In this context, the ultrasound-guided infraclavicular brachial plexus block has emerged as a commonly preferred approach, as it reliably anesthetizes the hand, forearm, and elbow while maintaining a favorable safety profile through real-time visualization of neural structures and avoidance of pleural and diaphragmatic involvement.<sup>[3]</sup>

Against this background of increasing reliance on ultrasound-guided regional anesthesia techniques, patient-related factors have become important determinants of perioperative block performance and recovery outcomes. Obesity is an increasingly prevalent global health condition and a clinically relevant modifier of perioperative anesthetic outcomes, with potential implications for both the performance and effectiveness of regional anesthesia.

<sup>[4]</sup> Earlier observational studies raised concerns regarding reduced peripheral nerve block success in obese patients. <sup>[5,6]</sup> Accumulating evidence indicates that, although increased body habitus may be associated with prolonged ultrasound visualization and needle advancement times, the use of modern ultrasound-guided techniques largely preserves block success rates, analgesic quality, opioid-sparing effects, and patient satisfaction across body mass index (BMI) categories.<sup>[7]</sup> Supporting this perspective, prospective randomized data in obese surgical populations have demonstrated that ultrasound-guided peripheral plane blocks can significantly reduce postoperative opioid consumption and pain intensity without increasing block-related complications. Parallel methodological advances in ultrasound imaging and interpretation have further refined sonoanatomic identification in patients with increased tissue depth, suggesting that obesity-related differences may manifest primarily as increased procedural complexity rather than diminished downstream analgesic or patient-reported outcomes.<sup>[8-10]</sup>

Nevertheless, this apparent equivalence in technical success may mask clinically relevant heterogeneity in postoperative pain experiences. Obesity is associated with chronic low-grade inflammation, altered nociceptive processing, and dysregulated neuroendocrine signaling, all of which may contribute to heightened pain sensitivity and increased analgesic requirements independent of block adequacy.<sup>[11]</sup> Moreover, obesity has been identified as an independent risk factor for intraoperative supplementation and acute block-related complications in anatomically challenging approaches, underscoring the need to distinguish procedural success from downstream analgesic and patient-reported outcomes.<sup>[4]</sup>

Contemporary perioperative care frameworks, including enhanced recovery after surgery (ERAS) protocols, increasingly prioritize patient-centered outcomes beyond immediate analgesia.<sup>[12]</sup> Postoperative pain trajectories, opioid consumption, and patient satisfaction are now recognized as key determinants of recovery quality and healthcare utilization. Despite this shift toward personalized perioperative medicine, evidence linking BMI stratification to integrated pain, analgesic consumption, and satisfaction outcomes following regional anesthesia remains limited.<sup>[10]</sup>

Existing literature on ultrasound-guided peripheral nerve blocks predominantly focuses on isolated perioperative endpoints, such as technical success rates or early postoperative pain scores, without adequately capturing the temporal evolution of pain or patient satisfaction beyond the

immediate postoperative period.<sup>[13]</sup> Assessment of longitudinal pain trajectories and patient-reported outcomes remains limited. In particular, BMI-stratified prospective and retrospective evaluations incorporating both short-term (1-week) and intermediate-term (1-month) patient-reported outcomes following ultrasound-guided infraclavicular brachial plexus block are notably scarce in the current literature.<sup>[10,14,15]</sup>

Addressing this knowledge gap may inform more accurate preoperative counseling and individualized perioperative analgesic strategies by clarifying the influence of BMI on both technical block performance and patient-centered postoperative outcomes, in line with the principles of precision perioperative medicine.

Therefore, this retrospective cohort study aimed to evaluate the association between BMI categories and integrated perioperative outcomes in adults undergoing upper extremity surgery with ultrasound-guided infraclavicular brachial plexus block. Specifically, we investigated whether BMI-related differences exist in block performance characteristics, postoperative analgesic consumption, pain intensity trajectories, patient satisfaction at 1-week and 1-month follow-up, and patient-reported preference for regional anesthesia in future surgical procedures.

## MATERIALS AND METHODS

### Study Design and Ethical Approval

This retrospective observational cohort study was approved by the Institutional Ethics Committee (Decision No: 301, Date: 05 December 2025). Adult patients who underwent upper extremity surgery under ultrasound-guided infraclavicular brachial plexus block were identified through the hospital's electronic anesthesia and surgical records. All procedures were conducted in accordance with the ethical standards of the institutional ethics committee and the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for written informed consent was waived.

### Study Population

Patients aged  $\geq 18$  years who underwent elective or urgent upper extremity surgery involving the hand, forearm, or elbow with ultrasound-guided infraclavicular brachial plexus block as the primary anesthetic technique were eligible for inclusion.

Exclusion criteria included incomplete medical records, conversion to general anesthesia, failed block requiring alternative anesthetic techniques, pre-existing chronic pain syndromes, regular opioid use, neurologic deficits affecting the operative limb, or contraindications to regional anesthesia.

### BMI Classification

BMI was calculated as weight (kg) divided by height squared ( $m^2$ ). Patients were stratified into three groups according

to World Health Organization criteria:

- BMI <25 kg/m<sup>2</sup> (normal weight),
- BMI 25–30 kg/m<sup>2</sup> (overweight),
- BMI ≥30 kg/m<sup>2</sup> (obese).

### Anesthetic Technique

Standard American Society of Anesthesiologists (ASA) monitoring, including electrocardiography, noninvasive blood pressure, and pulse oximetry, was applied to all patients. An intravenous line was established before block placement, and sedation was provided with midazolam and fentanyl as needed. Supplemental oxygen was administered via nasal cannula throughout the procedure.

All infraclavicular brachial plexus blocks were performed preoperatively under ultrasound guidance by experienced anesthesiologists using a high-frequency linear transducer. Patients were positioned supine with the ipsilateral arm abducted, and after aseptic preparation, the axillary artery and surrounding brachial plexus cords were identified in the infraclavicular region.

A single-injection technique was used, and local anesthetic was administered incrementally under continuous ultrasound visualization to ensure circumferential spread around the neural structures. Block performance characteristics, including procedural success and the need for intraoperative supplementation, were recorded.

A standardized mixture consisting of 0.2% bupivacaine combined with 0.4% lidocaine was used for all patients, resulting in a total volume of 30 mL. The total volume and concentrations were consistent across BMI groups and were not adjusted according to body mass index.

### Perioperative and Postoperative Management

Standardized intraoperative monitoring and postoperative analgesia protocols were applied across all BMI groups. Rescue analgesia was administered according to the institutional postoperative pain management protocol. When the Visual Analog Scale (VAS) score was ≥3, diclofenac sodium 75 mg or dexketoprofen 50 mg was given as first-line therapy. If the VAS score remained ≥3, paracetamol 1 g and tramadol 50 mg were administered. Rescue analgesic use and opioid requirements were routinely recorded as part of postoperative care.

### Outcome Measures

The primary outcome was postoperative pain intensity trajectory across BMI categories. Pain intensity was assessed using the Visual Analog Scale (VAS), defined as a 10-cm horizontal line ranging from 0 (no pain) to 10 (worst imaginable pain), at postoperative 0, 6, 12, and 24 hours.

Secondary outcomes included rescue analgesic requirement, opioid consumption, and patient-reported satisfaction. Postoperative satisfaction was assessed using a two-item Likert-type global satisfaction scale documented in routine clinical follow-up notes. The first item evalu-

ated overall satisfaction with the anesthetic technique and postoperative pain management (1 = very dissatisfied, 5 = very satisfied). The second item assessed willingness to choose regional anesthesia again for a similar procedure (1 = definitely no, 5 = definitely yes). Satisfaction scores were obtained from postoperative 1-week and 1-month follow-up records.

Demographic characteristics, anthropometric data, ASA physical status, operative duration, and sex-based comparisons were also analyzed.

### Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation (SD), median (minimum–maximum), or number and percentage, as appropriate. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests.

For normally distributed continuous variables, comparisons between independent groups were performed using the independent samples t-test. Non-normally distributed continuous variables were analyzed using the Mann–Whitney U test or the Kruskal–Wallis test, as appropriate. Categorical variables were compared using the chi-square test, and Fisher's exact test was applied when chi-square assumptions were not met.

All statistical analyses were conducted using SPSS Statistics software (version 27.0; IBM Corp., Armonk, NY, USA). A *p* value <0.05 was considered statistically significant.

## RESULTS

The study population consisted of 83 patients with a mean age of 40.4±16.0 years. The majority were male (66.3%). The mean BMI was 27.2±4.5 kg/m<sup>2</sup>. According to BMI classification, 22.9% of patients had BMI <25 kg/m<sup>2</sup>, 55.4% had BMI between 25–30 kg/m<sup>2</sup>, and 21.7% had BMI ≥30 kg/m<sup>2</sup> (Table 1).

There were no statistically significant differences among BMI <25, BMI 25–30, and BMI ≥30 groups with respect to age, sex distribution, height, or ASA physical status (*p*>0.05 for all). Body weight differed significantly across BMI groups (*p*<0.001), with the BMI ≥30 group exhibiting significantly higher body weight compared with both BMI <25 and BMI 25–30 groups. Additionally, the BMI 25–30 group had a significantly higher body weight than the BMI <25 group. No significant difference in operative time was observed between the groups (*p*=0.065). At postoperative hour 0, VAS scores were significantly higher in patients with BMI ≥ 30 compared with those with BMI 25–30 (*p*=0.040). No significant difference was observed between the BMI <25 group and the other BMI categories at this time point. VAS scores at postoperative hour 6 did not differ significantly among the BMI groups (*p*=0.742). At postoperative hour 12, the BMI ≥30 group demonstrated significantly higher VAS scores compared with the BMI 25–30 group (*p*=0.032). Similarly, at post-

**Table I.** Baseline demographic, clinical, and outcome characteristics of the study population

	Min-Max	Median	mean±SD, n (%)
Age (years)	18.0-78.0	38.0	40.4±16.0
Sex			
Male			55 (66.3)
Female			28 (33.7)
Height (cm)	145.0-195.0	170.0	170.6±9.4
Weight (kg)	34.0-130.0	78.0	79.3±15.1
BMI	16.2-45.0	27.0	27.2±4.5
BMI (kg/m <sup>2</sup> )			
<25			19 (22.9)
25-30			46 (55.4)
≥30			18 (21.7)
ASA Score			
I			20 (24.1)
II			62 (74.7)
III			1 (1.2)
Surgical duration (min)	20.0-205.0	105.0	105.9±43.4
VAS Score			
0. hr	0.00-4.00	0.00	0.51±0.85
6. hr	0.00-4.00	1.00	1.07±0.92
12. hr	0.00-5.00	2.00	2.17±1.02
24. hr	0.00-5.00	2.00	2.40±1.07
Rescue analgesia			
(-)			55 (66.3)
(+)			28 (33.7)
Opioid dose (mg)			
0			71 (85.5)
100			2 (2.4)
200			10 (12.0)
I-month overall satisfaction score	3.0-5.0	5.0	4.5±0.7
I-month satisfaction			
Neutral			11 (13.3)
Satisfied			20 (24.1)
Very satisfied			52 (62.7)
I-month preference for RA score	2.0-5.0	4.0	4.3±0.8
I-month preference for RA			
No			1 (1.2)
Neutral			14 (16.9)
Yes			29 (34.9)
Definitely yes			39 (47.0)

Data are presented as mean ± standard deviation (SD), median, minimum–maximum (Min–Max), or number (n) and percentage (%), as appropriate. BMI: Body mass index; ASA: American Society of Anesthesiologists physical status classification; VAS: Visual Analog Scale for pain; RA: Regional anesthesia.

operative hour 24, VAS scores were significantly higher in the BMI ≥ 30 group compared with both BMI <25 and BMI 25–30 groups ( $p=0.007$ ), whereas no significant difference was observed between BMI <25 and BMI 25–30 groups (Fig. 1). No statistically significant differences were found among BMI groups with respect to rescue analgesic use or opioid consumption ( $p>0.05$  for all comparisons). Patient satisfaction scores were significantly lower in the BMI ≥

30 group compared with both BMI <25 and BMI 25–30 groups ( $p<0.001$ ). No significant difference was observed between BMI <25 and BMI 25–30 groups. Similarly, one-month overall satisfaction scores were significantly higher in the BMI <25 and BMI 25–30 groups compared with the BMI ≥ 30 group ( $p<0.001$ ), while no significant difference was detected between BMI <25 and BMI 25–30 groups. Patients with BMI 25–30 demonstrated significantly higher

**Table 2.** Comparison of demographic, perioperative, and outcome variables across bmi groups

	BMI <25 (n:19)	BMI 25-30 (n=46)	BMI ≥30 (n=18)	p
Age				
(mean±SD)	35.1±15.6	41.1±15.7	44.1±16.9	0.169
Median	28.0	44.0	41.0	
Sex				
Male, n (%)	13 (68.4)	30 (65.2)	12 (66.7)	0.969
Female n (%)	6 (31.6)	16 (34.8)	6 (33.3)	
Height (cm)				
(mean ± SD)	173.0±12.1	169.5±8.8	170.9±7.8	0.409
Median	173.0	170.0	169.0	
Weight (kg)				
(mean ± SD)	65.7±11.2	77.8±8.6	97.6±14.4	0.000
Median	70.0 <sup>23</sup>	78.0 <sup>3</sup>	90.0	
ASA Score				
I, n (%)	6 (31.6)	12 (26.1)	2 (11.1)	0.310
II, n (%)	13 (68.4)	33 (71.7)	16 (88.9)	
III, n (%)	0 (0.0)	1 (2.2)	0 (0.0)	
Surgical duration (min)				
(mean±SD)	81.2±44.3	102.7±35.9	140.0±40.5	0.000
Median	75.0 <sup>3</sup>	105.0 <sup>3</sup>	152.5	
VAS Score				
0. hr (mean±SD)	0.63±1.07	0.30±0.59	0.89±1.02	0.040
Median	0.00	0.00 <sup>3</sup>	1.00	
6. hr (mean±SD)	1.00±1.05	1.04±0.82	1.22±1.06	0.742
Median	1.00	1.00	1.00	
12. hr (mean±SD)	2.11±1.10	1.98±0.93	2.72±1.02	0.032
Median	2.00	2.00 <sup>3</sup>	2.00	2.00
24. hr (mean±SD)	2.37±1.12	2.13±0.93	3.11±1.08	0.007
Median	2.00 <sup>3</sup>	2.00 <sup>3</sup>	4.00	
Rescue analgesia				
(-), n (%)	13 (68.4)	29 (63.0)	13 (72.2)	0.764
(+), n (%)	6 (31.6)	17 (37.0)	5 (27.8)	
Opioid dose (mg)				
0, n (%)	16 (84.2)	39 (84.8)	16 (88.9)	0.900
100, n (%)	0 (0.0)	2 (4.3)	0 (0.0)	
200, n (%)	3 (15.8)	5 (10.9)	2 (11.1)	
I-month overall satisfaction score				
(mean±SD)	4.6±0.5	4.8±0.4	3.6±0.8	0.000
Median	5.00	5.00	3.00 <sup>12</sup>	
I-month satisfaction				
Neutral, n (%)	0 (0.0)	0 (0.0)	11 (61.1)	0.000
Satisfied, n (%)	7 (36.8)	10 (21.7)	3 (16.7)	
Very satisfied, n (%)	12 (63.2)	36 (78.3)	4 <sup>12</sup> (22.2)	
I-month preference for RA score				
(mean±SD)	4.2±0.5	4.7±0.5	3.3±0.8	0.000
Median	4.00 <sup>2</sup>	5.00	3.00 <sup>12</sup>	
I-month preference for RA				
No, n (%)	0 (0.0)	0 (0.0)	1 (5.6)	0.000
Neutral, n (%)	1 (5.3)	0 (0.0)	13 (72.2)	
Yes, n (%)	13 (68.4)	15 (32.6)	1 (5.6)	
Definitely yes, n (%)	5 (26.3)	31 (67.4)	3 <sup>12</sup> (16.7)	

Data are presented as mean ± standard deviation (SD), median or number (n) and percentage (%), as appropriate. Comparisons among BMI groups were performed using the Kruskal–Wallis test for continuous variables and the chi-square ( $\chi^2$ ) test or Fisher's exact test, as appropriate, for categorical variables. A p value <0.05 was considered statistically significant. BMI: body mass index; ASA: American Society of Anesthesiologists physical status classification; VAS: Visual Analog Scale for pain; RA: Regional anesthesia.

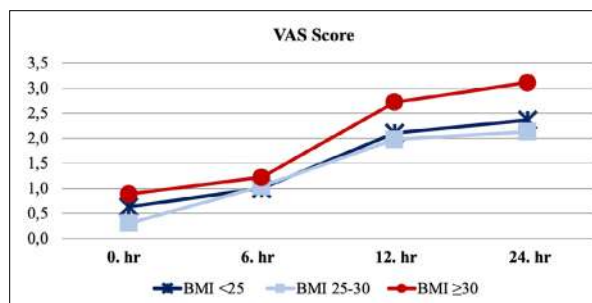
**Table 3.** Comparison of perioperative characteristics and postoperative pain outcomes between male and female patients

	Male (n=55)		Female (n=28)		p
	Mean±SD, n (%)	Median	Mean±SD, n (%)	Median	
Age (years)	34.7±13.2	32.0	51.4±15.6	51.0	0.000
Height (cm)	175.2±6.7	173.0	161.6±7.1	161.0	0.000
Weight (kg)	83.2±13.6	80.0	71.9±15.4	72.0	0.001
BMI	27.1±4.5	26.3	27.3±4.7	27.5	0.616
BMI<25	13 (23.6)		6 (21.4)		0.969
25-30	30 (54.5)		16 (57.1)		
≥30	12 (21.8)		6 (21.4)		
ASA Score					
I	17 (30.9)		3 (10.7)		0.042
II	38 (69.1)		24 (85.7)		
III	0 (0.0)		1 (3.6)		
Surgical duration (min)	102.1±46.4	105.0	113.2±36.4	110.0	0.274
VAS Score					
0. hr	0.6±1.0	0.0	0.3±0.5	0.0	0.313
6. hr	1.2±1.0	1.0	0.9±0.8	1.0	0.264
12. hr	2.3±1.1	2.0	2.0±0.9	2.0	0.453
24. hr	2.5±1.1	2.0	2.2±1.0	2.0	0.267
Rescue analgesia					
(-)	39 (70.9)		16 (57.1)		0.210
(+)	16 (29.1)		12 (42.9)		
Opioid dose (mg)					
0	50 (90.9)		21 (75.0)		0.051
100	0 (0.0)		2 (7.1)		
200	5 (9.1)		5 (17.9)		
I-month overall satisfaction score	4.4±0.8	5.0	4.6±0.6	5.0	0.197
I-month satisfaction					
Neutral	9 (16.4)		2 (7.1)		0.400
Satisfied	14 (25.5)		6 (21.4)		
Very satisfied	32 (58.2)		20 (71.4)		
I-month preference for RA score	4.2±0.8	4.0	4.4±0.8	5.0	0.231
I-month preference for RA					
No	0 (0.0)		1 (3.6)		0.522
Neutral	11 (20.0)		3 (10.7)		
Yes	21 (38.2)		8 (28.6)		
Definitely yes	23 (41.8)		16 (57.1)		

Values are presented as mean ± standard deviation (SD), median, or number (percentage), as appropriate. Continuous variables were compared between sexes using the Student's t-test or Mann-Whitney U test, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A p value <0.05 was considered statistically significant. VAS: Visual Analog Scale; BMI: Body mass index; ASA: American Society of Anesthesiologists physical status classification; RA: Regional anesthesia.

scores for subsequent preference for regional anesthesia score compared with both BMI <25 and BMI ≥30 groups (p<0.001). Additionally, the BMI <25 group showed significantly higher subsequent preference for regional anesthesia scores compared with the BMI ≥30 group. At one month, patients' subsequent preference for regional anesthesia (patient-reported outcome measure, PROM) scores were significantly higher in the BMI <25 and BMI 25–30 groups compared with the BMI ≥30 group (p<0.001), with no significant difference between the BMI <25 and BMI 25–30 groups (Table 2).

Female patients were significantly older than male patients



**Figure 1.** Postoperative VAS scores across BMI groups during the first 24 hours. VAS: Visual Analog Scale; BMI: Body Mass Index.

( $p < 0.05$ ). Females also had significantly lower height and body weight compared with males ( $p < 0.05$  for both). However, BMI values and BMI distribution did not differ significantly between sexes ( $p > 0.05$ ). ASA scores were significantly higher in female patients ( $p < 0.05$ ). Operative duration did not differ significantly between male and female patients. Postoperative VAS scores at 0, 6, 12, and 24 hours showed no significant sex-related differences. Similarly, rescue analgesic use, opioid consumption, patient satisfaction, one-month overall satisfaction, and subsequent preference for regional anesthesia score at one month did not differ significantly between males and females ( $p > 0.05$  for all) (Table 3).

## DISCUSSION

This retrospective cohort study demonstrates that BMI serves as a critical determinant of perioperative outcomes following ultrasound-guided infraclavicular brachial plexus block, encompassing broader perioperative clinical and analgesic outcomes. While our findings reveal comparable block success rates across BMI categories, postoperative pain trajectories, analgesic consumption patterns, and patient satisfaction scores exhibit significant deterioration with advancing BMI classification. These observations underscore the importance of viewing BMI not solely as a demographic variable, but rather as an independent perioperative outcome determinant informing tailored therapeutic strategies.

The time-dependent trajectory of postoperative pain intensity in our cohort demonstrates a distinct pattern of BMI-stratified heterogeneity, particularly pronounced at the 24-hour interval where patients with BMI  $\geq 30$  kg/m<sup>2</sup> demonstrated VAS scores of  $3.11 \pm 1.89$ , substantially exceeding those of patients with lower BMI. This finding aligns with contemporary evidence from Zengin et. al.,<sup>[16]</sup> who similarly documented elevated VAS scores at 4, 12, and 48 hours in obese patients receiving thoracic paravertebral block anesthesia. However, our investigation further elaborates this time-course characterization, demonstrating that BMI-related pain differences remain evident beyond the early postoperative period, extending through the 12- and 24-hour recovery intervals.

The heterogeneous pain profile observed across BMI categories cannot be fully explained by variability in block technical success alone, suggesting that obesity influences adverse pain-related outcomes primarily through alterations in nociceptive processing rather than regional anesthesia performance in itself. Growing evidence suggests that chronic low-grade inflammation associated with adipose tissue, marked by increased interleukin-6, tumor necrosis factor- $\alpha$ , and C-reactive protein levels, together with altered neuroendocrine signaling, promotes heightened nociceptive sensitivity independent of regional anesthetic effectiveness.<sup>[17]</sup> De Cassai et. al.<sup>[4]</sup> underscore this mechanistic distinction, emphasizing that altered bioactive adipokine profiles in obese patients predispose toward

enhanced nociceptive processing and attenuated analgesic responsiveness. This represents a key pathophysiologic mechanism acting independently of technical block success.

These clinical findings are supported by emerging mechanistic data indicating that obesity alters nociceptive processing and inflammatory signaling, thereby modifying postoperative pain and patient-reported outcomes independently of block performance. Lin et. al.<sup>[18]</sup> report that, despite advances in ultrasound imaging, identification of neural structures in obese patients remains limited by adipose-related acoustic attenuation. The pattern observed in our study, with technically successful blocks accompanied by higher postoperative pain in patients with BMI  $\geq 30$  at 24 hours, indicates that adequate sonographic visualization does not reliably predict anesthetic effectiveness in the context of obesity-related inflammatory changes.

Obesity-related pain phenotypes arise from the integrated effects of genetic susceptibility, neuroendocrine dysregulation, and altered peripheral nociceptive signaling. Emerging mechanistic studies indicate that genetic variants influencing  $\mu$ -opioid receptor expression in obese individuals are associated with increased receptor levels together with reduced pain thresholds and higher opioid requirements.<sup>[19]</sup> The progressive increase in pain observed in our cohort, most evident at 24 hours in patients with BMI  $\geq 30$ , likely reflects the interaction between pre-existing obesity-related inflammation and the acute inflammatory response to surgery.

Zengin et. al.<sup>[16]</sup> demonstrated through genetic polymorphism screening that elevated mu receptor expression in morbidly obese patients correlated paradoxically with increased morphine and fentanyl consumption requirements, suggesting that polymorphism-related alterations in opioid receptor physiology may contribute to the enhanced analgesic demands observed in our obese cohort. Furthermore, altered nociceptor sensitization mediated by chronic elevations in inflammatory mediators leads to persistent hyperalgesia that perioperative regional anesthesia, even when technically successful, may not fully mitigate.

De Cassai et. al.<sup>[4]</sup> report that local anesthetic distribution in obesity is better predicted by lean body weight rather than total body weight (TBW), such that TBW-based dosing may result in relatively lower effective exposure in obese patients, contributing to reduced analgesic effectiveness despite technical block success. Additionally, increased adipose tissue depth during infraclavicular block in obese patients may compromise effective local anesthetic distribution, as shown by Kavakli et. al.,<sup>[8]</sup> who demonstrated progressive ultrasound signal attenuation with increasing fatty tissue thickness.

An important finding of our study relates to patients' subsequent preference for regional anesthesia as a PROM. This preference was markedly higher among patients with BMI  $< 25$  (94.7%) compared with those with BMI  $\geq 30$  (27.8%), reflecting clinically relevant variation in patient-perceived benefit across BMI categories. This difference is consistent

with the observed variation in postoperative pain intensity and suggests that procedural block success, in the absence of effective pain control, may not be sufficient to ensure patient satisfaction.

Admiraal et al.<sup>[14]</sup> support the greater incorporation of PROMs in regional anesthesia research, alongside technical metrics such as block success rate and procedure duration. Consistent with this approach, our findings show that BMI-related differences in patient-reported satisfaction occur despite similar block success and are more closely related to postoperative pain patterns than to procedural block performance.

Current perioperative care models, including ERAS protocols, increasingly emphasize individualized, patient-centered outcomes.<sup>[12]</sup> In obese patients undergoing infraclavicular brachial plexus block, several targeted strategies may improve analgesic effectiveness and patient experience. Local anesthetic dosing should be guided by lean body weight rather than total body weight, particularly for lipophilic agents such as bupivacaine, to better reflect pharmacokinetic behavior in obesity.<sup>[4]</sup> In addition, ultrasound-guided block performance in obese patients should be optimized through technique modifications.<sup>[20]</sup> Optimization of ultrasound settings and patient positioning may facilitate target visualization, and regional anesthesia is best applied within an opioid-sparing multimodal strategy; in bariatric populations, Baytar et al.<sup>[21]</sup> reported improved postoperative respiratory outcomes and reduced opioid consumption with a modified thoracoabdominal nerve block approach.

By extending follow-up beyond the early postoperative period and incorporating patient-reported outcome measures, this study complements existing infraclavicular block literature, which has largely focused on technical success and early pain. In this context, Saranlal et al.<sup>[15]</sup> evaluated infraclavicular block performance across BMI groups but did not assess postoperative pain, analgesic use, or patient satisfaction, whereas our analysis integrates both technical and patient-centered outcomes.

These findings have important implications for the perioperative management of obese patients undergoing regional anesthesia. Preoperative evaluation should acknowledge that technical block success may not ensure adequate postoperative analgesia in obese patients, and that multimodal pain management may be required. Local anesthetic dosing is better based on lean body weight rather than total body weight, with consideration of agent-specific pharmacokinetic properties and monitoring for local anesthetic systemic toxicity; De Cassai et al.<sup>[4]</sup> provide evidence-based dosing frameworks stratified by BMI category and specific local anesthetic agents. In addition, the use of anti-inflammatory medications, perineural adjuvants, and supplementary regional techniques, when feasible, should be incorporated into perioperative care pathways to improve analgesic outcomes in obese patients.

Finally, PROMs from our study indicate that the quality of

analgesia during the first 24 postoperative hours is closely associated with subsequent patient experience. Optimizing early pain control in the post-anesthesia care unit may improve patient satisfaction and subsequent patient-reported outcomes related to regional anesthesia.

### Limitations

This study has several limitations. Its retrospective design introduces potential sources of bias, and the relatively small sample size with limited representation of patients with BMI >40 kg/m<sup>2</sup> reduces the precision of subgroup analyses. Pain was assessed only with the visual analog scale, without quantitative sensory or functional measures, and sensory block distribution was not systematically evaluated. In addition, although all procedures involved upper extremity surgeries within the infraclavicular block distribution area, variability in surgical type may have influenced postoperative analgesic requirements and could represent a potential confounding factor. Finally, the restriction to upper extremity surgery limits the generalizability of these findings to other surgical settings.

### CONCLUSION

This study indicates that obesity influences infraclavicular brachial plexus block outcomes through mechanisms that extend beyond technical block success, with higher postoperative pain and lower patient-reported satisfaction observed in patients with higher BMI. These findings support the need for BMI-specific approaches to perioperative pain management. Future prospective studies should evaluate weight-adjusted dosing strategies, optimized block techniques, multimodal analgesia, and longitudinal patient-reported outcomes, while also exploring the role of inflammatory and neurobiological mechanisms underlying altered pain responses in obesity. Such work may help to define more individualized perioperative strategies that improve both analgesic effectiveness and patient-centered outcomes in this patient group.

### Ethics Committee Approval

The study was approved by the SBÜ Istanbul Training and Research Hospital Ethics Committee (Date: 05.12.2025, Decision No: 301).

### Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: G.C.; Design: G.C., E.E.; Supervision: A.S.; Fundings: G.C., E.E.; Materials: A.T., E.E., M.K.; Data collection &/or processing: E.E., M.K.; Analysis and/or interpretation: A.T., G.C.; Literature search: G.C., M.K., A.S.; Writing: G.C., A.S.; Critical review: A.S.

### Conflict of Interest

The authors declare that they have no conflicts of interest.

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## İnfraklaviküler Brakial Pleksus Bloğu Uygulanan Hastalarda Vücut Kitle İndeksi ile Postoperatif Ağrı Sonuçları ve Hasta Memnuniyeti Arasındaki İlişki

**Amaç:** Obezite, rejyonel anestezi sonrası postoperatif ağrı ve hasta bildiriyle ölçülen sonuçları, teknik blok başarısının ötesindeki mekanizmalar yoluyla etkileyebilir. Bu çalışmada, ultrason eşliğinde infraklaviküler brakial pleksus bloğu uygulanan üst ekstremitte cerrahisi hastalarında vücut kitle indeksi (VKİ) kategorileri ile perioperatif sonuçlar arasındaki ilişki değerlendirilmiştir.

**Gereç ve Yöntem:** Bu retrospektif gözlemsel kohort çalışmasına, el, önkol veya dirsek cerrahisi için primer anestezi tekniği olarak ultrason eşliğinde infraklaviküler brakial pleksus bloğu uygulanan 83 erişkin hasta ( $\geq 18$  yaş) dahil edildi. Hastalar VKİ'ye göre  $<25$  kg/m<sup>2</sup> (n=19), 25–30 kg/m<sup>2</sup> (n=46) ve  $\geq 30$  kg/m<sup>2</sup> (n=18) olarak sınıflandırıldı. Postoperatif ağrı şiddeti, Görsel Analog Skala (VAS; 0–10) kullanılarak 0., 6., 12. ve 24. saatlerde değerlendirildi. İkincil sonlanım ölçütleri; kurtarma analjezi gereksinimi, opioid tüketimi ve hasta bildiriyle ölçülen sonuçları (PROM'lar) kapsadı. PROM'lar, 1. hafta ve 1. ayda hasta memnuniyeti ile 1. ayda gelecekte rejyonel anestezi tercihine ilişkin değerlendirmeleri içerdi.

**Bulgular:** Demografik özellikler, BMI grupları arasında benzerdi ( $p>0.05$ ). Postoperatif VAS skorları VKİ'ye göre 0., 12. ve 24. saatlerde anlamlı farklılık gösterdi; en yüksek ağrı özellikle 24. saatte VKİ  $\geq 30$  olan hastalarda saptandı ( $3.11 \pm 1.89$ ), 6. saat skorları ise benzerdi. Kurtarma analjezi kullanımı ve opioid tüketimi gruplar arasında farklılık göstermedi. Hasta memnuniyeti ve 1. ayda rejyonel anesteziyi tekrar tercih etme skorları VKİ  $\geq 30$  grubunda, VKİ  $<25$  ve VKİ 25–30 gruplarına kıyasla anlamlı olarak daha düşüktü ( $p<0.001$ ).

**Sonuç:** Yüksek VKİ, ultrason eşliğinde infraklaviküler brakial pleksus bloğu sonrasında daha olumsuz ağrı seyri ve daha düşük hasta bildiriyle ölçülen memnuniyet ile ilişkili bulunmuştur; buna karşın kurtarma analjezi ve opioid kullanımı VKİ grupları arasında benzerdir. Bu bulgular, bireyselleştirilmiş perioperatif analjezik planlama ve hasta odaklı sonuçların iyileştirilmesi açısından VKİ sınıflamasının dikkate alınması gerektiğini düşündürmektedir.

**Anahtar Sözcükler:** İnfraklaviküler brakial pleksus bloğu; postoperatif ağrı; rejyonel anestezi; vücut kitle indeksi.

# Impact of Ovarian Conservation on Sexual Function and Menopausal Symptoms After Hysterectomy in Premenopausal Women: A Retrospective Comparative Study

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**Keywords:** FSFI; hysterectomy; menopause; oophorectomy; ovarian conservation; premenopausal; quality of life; sexual function.



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## ABSTRACT

**Objective:** To conduct a quantitative comparison of long-term sexual function and the severity of menopausal symptoms in premenopausal women who have undergone hysterectomy with ovarian conservation versus those who have undergone hysterectomy with bilateral salpingo-oophorectomy (BSO).

**Methods:** This retrospective study encompassed 160 premenopausal women who had undergone hysterectomy for benign reasons at least one year prior. Participants were categorized into two cohorts: The Hysterectomy with Ovarian Conservation (HOC) group (n=80) and the Hysterectomy with Bilateral Salpingo-Oophorectomy (H-BSO) group (n=80). The study employed validated instruments, namely the Female Sexual Function Index (FSFI) and the Menopause Rating Scale (MRS), to gather data on sexual function and menopausal symptoms. Demographic and clinical information was extracted from patient records. Statistical analyses were conducted using independent samples t-tests and chi-square tests.

**Results:** Both groups were comparable in terms of mean age, BMI, and primary indication for hysterectomy ( $p>0.05$ ). The HOC group reported significantly higher (better) total FSFI scores compared to the H-BSO group ( $27.8\pm 4.1$  vs.  $18.5\pm 5.5$ ;  $p<0.001$ ). Significant differences were observed across all FSFI domains, including desire, arousal, lubrication, orgasm, satisfaction, and pain (all  $p<0.001$ ). Conversely, the H-BSO group reported significantly higher (worse) total MRS scores ( $23.2\pm 6.8$  vs.  $9.7\pm 4.5$ ;  $p<0.001$ ), with pronounced differences in somatic, psychological, and urogenital subscales.

**Conclusion:** Ovarian conservation at the time of hysterectomy in premenopausal women is strongly and significantly associated with preserved sexual function and a substantially lower burden of menopausal symptoms in the long term. These findings provide crucial quantitative evidence to support shared decision-making, advocating for ovarian conservation in appropriate candidates to protect long-term quality of life.

## INTRODUCTION

Hysterectomy is among the most frequently performed gynecological surgeries globally, with millions of procedures conducted annually.<sup>[1]</sup> For premenopausal women undergoing this surgery for benign reasons, a pivotal intraoperative decision involves whether to conduct a concurrent bilateral salpingo-oophorectomy (BSO). This decision poses a complex clinical challenge, requiring a balance

between the prophylactic advantage of reducing future ovarian cancer risk and the physiological implications of iatrogenic menopause.<sup>[2,3]</sup>

The surgical removal of ovaries in premenopausal women results in an immediate and irreversible cessation of endogenous estrogen and androgen production, thereby inducing surgical menopause.<sup>[4]</sup> The associated consequences are well-documented, including an elevated long-

term risk of cardiovascular disease, osteoporosis, cognitive decline, and all-cause mortality.<sup>[5-8]</sup> Additionally, the emergence of severe vasomotor and urogenital symptoms can significantly affect a woman's quality of life.<sup>[9,10]</sup>

The impact on sexual function is of particular significance. Ovarian hormones play a vital role in sustaining vaginal lubrication, pelvic blood flow, and sexual desire. The sudden loss of these hormones can result in dyspareunia, reduced libido, and challenges with arousal and orgasm, leading to considerable personal and interpersonal distress.<sup>[11,12]</sup> Although the practice of prophylactic BSO has been decreasing in recent years, particularly among women at average risk for ovarian cancer,<sup>[13,14]</sup> the decision-making process frequently lacks comprehensive, quantitative data to provide to patients concerning long-term sexual well-being.

Although the advantages of ovarian conservation are widely recognized,<sup>[15]</sup> there remains a necessity for high-quality comparative studies employing validated, multi-dimensional tools to accurately measure variations in sexual function and menopausal burden. The Female Sexual Function Index (FSFI) and the Menopause Rating Scale (MRS) are validated instruments that facilitate such comprehensive assessments.<sup>[16-18]</sup>

This study aims to address the existing gap by retrospectively comparing outcomes in two well-defined cohorts of premenopausal women: Those who underwent hysterectomy with ovarian conservation and those who underwent hysterectomy with bilateral salpingo-oophorectomy (BSO). To our knowledge, this represents one of the largest comparative analyses utilizing validated Female Sexual Function Index (FSFI) and Menopause Rating Scale (MRS) tools within a homogeneous premenopausal cohort. The primary objective of this study is to furnish clear, quantitative evidence regarding the long-term impact of oophorectomy on sexual function and menopausal symptoms in this patient population, thereby enabling clinicians and patients to engage in more informed shared decision-making.

## MATERIALS AND METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of Health Sciences University Gazi Yaşargil Training and Research Hospital (No: 589, Date: 19/09/2025). Informed consent was obtained from all participants prior to data collection.

### Study Design and Patient Population

This retrospective study was conducted by reviewing medical records from a tertiary care hospital. The study protocol was approved by the Institutional Review Board.

A cohort of 160 women who underwent hysterectomy for benign gynecological conditions between January 2018 and December 2022 was included in this study. The in-

clusion criteria stipulated that participants must be premenopausal at the time of surgery, as confirmed by patient history and/or hormonal levels, and aged between 40 and 50 years. This age range was selected to ensure premenopausal status while encompassing women most likely to undergo hysterectomy for benign indications. Eligible surgeries were required to be performed for benign causes such as uterine fibroids, abnormal uterine bleeding, or adenomyosis, and participants were required to have a minimum of 12 months of follow-up post-surgery.

Exclusion criteria comprised any history of gynecological or other malignancy, a pre-existing diagnosis of sexual dysfunction or severe psychiatric disorder, postmenopausal status at the time of surgery, and incomplete medical records. Patients were divided into two groups:

- **HOC Group (Hysterectomy with Ovarian Conservation):** n=80 women who underwent total hysterectomy with conservation of at least one ovary.
- **H-BSO Group (Hysterectomy with Bilateral Salpingo-Oophorectomy):** n=80 women who underwent total hysterectomy with concurrent BSO.

Demographic data, including age and BMI, as well as surgical details such as the type of hysterectomy and the indication for surgery, alongside clinical history, were extracted from electronic medical records. Subsequently, eligible patients were contacted via telephone by a trained research nurse. Upon obtaining verbal consent, participants were administered the validated FSFI and MRS questionnaires.

### Outcome Measures

- **Female Sexual Function Index (FSFI):** A 19-item validated questionnaire that assesses female sexual function over the past 4 weeks across six domains: Desire, arousal, lubrication, orgasm, satisfaction, and pain.<sup>[16]</sup> The total score ranges from 2 to 36, with higher scores indicating better sexual function. A total score of  $\leq 26.55$  is commonly used as a clinical cutoff for diagnosing female sexual dysfunction (FSD).<sup>[17]</sup>
- **Menopause Rating Scale (MRS):** An 11-item validated questionnaire that assesses the severity of age-related menopausal symptoms across three domains: Somatic (e.g., hot flashes, heart discomfort), psychological (depressive mood, irritability), and urogenital (vaginal dryness, bladder problems). Higher scores indicate greater symptom severity.<sup>[18]</sup>

### Statistical Analysis

All statistical analyses were performed using SPSS for Windows, Version 27.0 (IBM Corp., Armonk, NY). Continuous variables were presented as mean  $\pm$  standard deviation (SD) and compared between groups using an independent samples t-test. Categorical variables were presented as frequencies and percentages (%) and compared using the Chi-square test or Fisher's exact test, as appropriate. A p-value of  $<0.05$  was considered statistically significant for all analyses.

## RESULTS

The demographic and clinical characteristics of the 160 patients are presented in Table 1. There were no statistically significant differences between the HOC and H-BSO groups in terms of mean age, BMI, or the primary indication for hysterectomy, indicating that the two groups were well-matched at baseline. The most common indication for surgery in both groups was uterine fibroids.

### Sexual Function Outcomes (FSFI)

The comparison of FSFI scores is shown in Table 2. The HOC group demonstrated significantly better sexual function across all domains. The mean total FSFI score was 27.8 in the HOC group, compared to a severely dysfunc-

tional score of 18.5 in the H-BSO group ( $p < 0.001$ ). The largest differences were observed in the domains of lubrication and desire. Importantly, 68.8% of women in the H-BSO group had an FSFI score below the clinical cutoff for FSD ( $\leq 26.55$ ), compared to only 22.5% in the HOC group.

### Menopausal Symptom Outcomes (MRS)

The burden of menopausal symptoms was significantly higher in the H-BSO group, as detailed in Table 3. The mean total MRS score for the H-BSO group was 23.2, indicating severe symptomatology, whereas the HOC group had a mean score of 9.7, indicating mild symptoms ( $p < 0.001$ ). The most striking differences were seen in the somatic (hot flashes, sweating) and urogenital (vaginal dryness, bladder problems) subscales.

**Table 1.** Baseline demographic and clinical characteristics of the study groups

Characteristic	HOC Group (n=80)	H-BSO Group (n=80)	p-value
Age (years), mean $\pm$ SD	46.2 $\pm$ 3.1	46.8 $\pm$ 2.9	0.215
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	28.1 $\pm$ 4.5	27.7 $\pm$ 4.9	0.582
Indication for Hysterectomy, n (%)			0.881
Uterine Fibroids	45 (56.3%)	43 (53.8%)	
Abnormal Uterine Bleeding	21 (26.3%)	23 (28.8%)	
Adenomyosis/Endometriosis	14 (17.5%)	14 (17.5%)	
Type of Hysterectomy, n (%)			0.745
Abdominal	35 (43.8%)	38 (47.5%)	
Laparoscopic/Robotic	45 (56.3%)	42 (52.5%)	

HOC: Hysterectomy with Ovarian Conservation; H-BSO: Hysterectomy with Bilateral Salpingo-Oophorectomy.

**Table 2.** Comparison of Female Sexual Function Index (FSFI) scores

FSFI Domain	HOC Group (n=80)	H-BSO Group (n=80)	p-value
Desire, mean $\pm$ SD	4.5 $\pm$ 0.9	2.8 $\pm$ 1.1	<0.001
Arousal, mean $\pm$ SD	4.8 $\pm$ 0.8	3.1 $\pm$ 1.2	<0.001
Lubrication, mean $\pm$ SD	4.9 $\pm$ 1.0	2.5 $\pm$ 1.3	<0.001
Orgasm, mean $\pm$ SD	4.6 $\pm$ 1.1	3.4 $\pm$ 1.4	<0.001
Satisfaction, mean $\pm$ SD	4.7 $\pm$ 0.9	3.5 $\pm$ 1.2	<0.001
Pain, mean $\pm$ SD	4.3 $\pm$ 1.2	3.2 $\pm$ 1.5	<0.001
Total FSFI Score, mean $\pm$ SD	27.8 $\pm$ 4.1	18.5 $\pm$ 5.5	<0.001

**Table 3.** Comparison of Menopause Rating Scale (MRS) scores

MRS Domain	HOC Group (n=80)	H-BSO Group (n=80)	p-value
Somatic Score, mean $\pm$ SD	3.1 $\pm$ 1.8	9.5 $\pm$ 3.2	<0.001
Psychological Score, mean $\pm$ SD	4.2 $\pm$ 2.1	7.9 $\pm$ 2.9	<0.001
Urogenital Score, mean $\pm$ SD	2.4 $\pm$ 1.5	5.4 $\pm$ 2.3	<0.001
Total MRS Score, mean $\pm$ SD	9.7 $\pm$ 4.5	23.2 $\pm$ 6.8	<0.001

## DISCUSSION

This study presents compelling quantitative evidence indicating that the preservation of ovaries during hysterectomy in premenopausal women significantly benefits the maintenance of long-term sexual function and alleviates menopausal symptoms.<sup>[19-21]</sup> Our findings reveal a marked disparity in quality of life outcomes, highlighting the critical importance of considering “the ovarian factor” in surgical decision-making.

The markedly lower FSFI scores observed in the H-BSO group directly reflect the physiological consequences of surgical menopause. The sudden cessation of ovarian estrogen and androgen production results in vaginal atrophy, diminished blood flow, and reduced lubrication, as evidenced by the poor scores in the lubrication and pain domains.<sup>[22,23]</sup> Additionally, ovarian androgens are crucial for female libido; their removal directly contributes to the decreased desire and arousal reported by the H-BSO group.<sup>[24]</sup> The mean total FSFI score of 18.5 in this group is significantly below the clinical threshold for FSD, indicating that the majority of these women experience clinically significant sexual dysfunction.<sup>[25]</sup>

The pronounced menopausal symptoms observed in the H-BSO group, with a mean MRS score of 23.2, represent an anticipated yet significant finding. The abrupt hormonal deprivation leads to severe vasomotor symptoms, psychological distress, and urogenital atrophy, collectively diminishing overall well-being.<sup>[26]</sup> Conversely, the HOC group reported only mild symptoms, suggesting that their preserved ovaries continued to offer essential hormonal support, even following the removal of the uterus.

A noteworthy aspect of our findings is that while significantly better than the BSO group, a subset of women in the HOC group (22.5%) still reported FSFI scores indicative of sexual dysfunction. This suggests that hysterectomy itself, even with ovarian preservation, is not entirely benign in its impact on sexual function.<sup>[27]</sup> Potential explanations include alteration of pelvic anatomy, disruption of nerve pathways during cervical dissection, or loss of uterine-specific contributions to orgasm.<sup>[28]</sup> This highlights that while preserving hormones is paramount, the uterus itself may play a role in sexual response, a factor requiring further investigation.

From a clinical perspective, these data should be integral to contemporary shared decision-making practices. The traditional rationale for prophylactic bilateral salpingo-oophorectomy (BSO) has been the reduction of ovarian cancer risk. However, for women at average risk, the absolute risk of developing ovarian cancer is relatively low.<sup>[29]</sup> Our study reveals that the outcome of this risk-reducing surgery is not merely a possibility but a certainty: It induces significant, measurable declines in sexual function and overall quality of life. Clinicians can now utilize this quantitative data to counsel patients more effectively, framing the decision not as “preventing a future risk” versus “no benefit,” but as “preventing a small future risk”

versus “preserving definite, high-quality years of sexual and psychological well-being.”<sup>[30]</sup>

The strengths of this study include its well-defined cohort and the utilization of internationally validated, multi-dimensional questionnaires (FSFI and MRS) to capture patient-reported outcomes.<sup>[16-18]</sup> The primary limitation is its retrospective design, which introduces the potential for recall bias and depends on patient self-reporting. Additionally, the absence of pre-operative baseline FSFI or MRS scores precluded a longitudinal assessment of change. Future prospective studies should aim to collect baseline data to more accurately measure post-surgical outcomes.<sup>[31]</sup> And as this study was based on questionnaire data, serum estrogen levels and other hormonal or biochemical parameters were not assessed, which limits the ability to directly correlate our findings with physiological mechanisms.

## CONCLUSION

In premenopausal women undergoing hysterectomy for benign conditions, the decision to preserve the ovaries is unequivocally linked to enhanced long-term sexual function and a significantly reduced incidence of menopausal symptoms. The removal of healthy ovaries results in severe, clinically significant sexual dysfunction and menopausal distress in the majority of patients. This study offers robust, quantitative evidence supporting the paradigm of ovarian conservation whenever feasible in average-risk premenopausal women, emphasizing the importance of long-term quality of life in the shared decision making process.<sup>[32]</sup>

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### Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

### Ethics Committee Approval

The study protocol was reviewed and approved by the Institutional Review Board of Health Sciences University Gazi Yaşargil Training and Research Hospital (Date: 19.09.2025, Decision No: 589).

### Informed Consent

Informed consent was obtained from all participants prior to data collection.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: G.C.C., K.A.; Design: G.C.C., K.A.; Supervision: A.D.E., B.C., K.C.Y.; Fundings: P.B.I., B.C.; Materials: E.A,

K.C.Y.; Data collection &/or processing: G.C.C., K.A., K.C.Y.; Analysis and/or interpretation: P.B.I., B.C.; Literature search: G.C.C., K.A.; Writing: G.C.C., K.A.; Critical review: P.B.I., B.C., K.C.Y.

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### Conflict of Interest

None declared.

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## Premenopozal Kadınlarda Histerektomi Sonrası Overyen Korumanın Cinsel Fonksiyon ve Menopoz Semptomları Üzerine Etkisi: Retrospektif Karşılaştırmalı Bir Çalışma

**Amaç:** Premenopozal kadınlarda overlerin korunduğu histerektomi ile bilateral salpingo-ooferektomi (BSO) yapılan histerektomi sonrası uzun dönem cinsel fonksiyon ve menopoz semptomlarının şiddetini nicel olarak karşılaştırmak.

**Gereç ve Yöntem:** Bu retrospektif çalışmaya, benign nedenlerle en az bir yıl önce histerektomi geçirmiş 160 premenopozal kadın dahil edildi. Katılımcılar iki gruba ayrıldı: Overyen Koruma ile Histerektomi (HOC) grubu (n=80) ve Bilateral Salpingo-Ooferektomi ile Histerektomi (H-BSO) grubu (n=80). Cinsel fonksiyon ve menopoz semptomlarına ilişkin veriler, geçerliliği kanıtlanmış araçlar olan Kadın Cinsel Fonksiyon İndeksi (FSFI) ve Menopoz Değerlendirme Ölçeği (MRS) kullanılarak toplandı. Demografik ve klinik bilgiler hasta kayıtlarından elde edildi. İstatistiksel analizler bağımsız örneklem t-testi ve ki-kare testi ile gerçekleştirildi.

**Bulgular:** Her iki grup yaş ortalaması, BKİ ve histerektomi endikasyonu açısından karşılaştırılabilir bulundu ( $p>0.05$ ). HOC grubunun toplam FSFI skorları H-BSO grubuna göre anlamlı derecede daha yüksek (daha iyi) idi ( $27.8\pm 4.1$ 'e karşı  $18.5\pm 5.5$ ;  $p<0.001$ ). İstek, uyarılma, lubrikasyon, orgazm, tatmin ve ağrı dâhil tüm FSFI alt alanlarında anlamlı farklılıklar izlendi (tüm  $p<0.001$ ). Buna karşılık, H-BSO grubunun toplam MRS skorları anlamlı derecede daha yüksek (daha kötü) bulundu ( $23.2\pm 6.8$ 'e karşı  $9.7\pm 4.5$ ;  $p<0.001$ ) ve somatik, psikolojik ve ürogenital alt ölçeklerde belirgin farklılıklar mevcuttu.

**Sonuç:** Premenopozal kadınlarda histerektomi sırasında overlerin korunması, uzun dönemde cinsel fonksiyonun devamlılığı ve menopoz semptomlarının belirgin şekilde daha düşük olması ile güçlü ve anlamlı şekilde ilişkilidir. Bu bulgular, uygun adaylarda overlerin korunmasını savunarak uzun dönem yaşam kalitesini korumaya yönelik paylaşımlı karar verme sürecine önemli nicel kanıt sunmaktadır.

**Anahtar Sözcükler:** Cinsel Fonksiyon; FSFI; histerektomi; menopoz; ooferektomi; overyen koruma; premenopozal; yaşam kalitesi.

# Analysis of Causes and Risk Factors for Conversion from Laparoscopic to Open Cholecystectomy

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## ABSTRACT

**Objective:** This study aimed to identify the causes of conversion from laparoscopic cholecystectomy (LC) to open cholecystectomy (OC) and to determine the demographic characteristics, conversion rate, and associated risk factors.

**Methods:** A total of 4,165 patients who underwent cholecystectomy for symptomatic cholelithiasis at our institution between January 2016 and December 2021 were retrospectively analyzed. Demographic characteristics, indications for conversion, and conversion rates were evaluated in 74 patients who required conversion from LC to OC.

**Results:** Among the 4,165 patients, 74 (1.8%) required conversion from LC to OC. Of these, 33 (44.6%) were female and 41 (55.4%) were male. The mean age was 56 years (40–82), and the mean BMI was 30 kg/m<sup>2</sup> (25–43). Comorbidities were present in 44 patients (59.4%). The main reasons for conversion were adhesions and fibrosis due to prior surgery (n=41, 55.4%), acute cholecystitis (n=19, 25.7%), inability to clearly identify Calot's triangle (n=3, 4.1%), bleeding from the cystic artery or gallbladder bed/liver (n=4, 5.4%), luminal organ injury (n=4, 5.4%), and biliary tract injury (n=3, 4.1%). Intraoperative complications occurred in 11 patients (14.9%), while postoperative complications occurred in 8 patients (10.2%). No patient required reoperation, and no mortality was observed. The mean length of hospital stay was 2.2 days (1–12).

**Conclusion:** LC remains the preferred surgical approach for symptomatic gallstones. However, in patients with significant risk factors, persistent attempts to complete the procedure laparoscopically may increase morbidity. Timely conversion to OC and increasing surgical experience may help reduce complication rates.

## INTRODUCTION

Gallbladder surgery for cholelithiasis is among the most frequently performed procedures in general surgery. Since the 1980s, laparoscopic cholecystectomy (LC) has largely replaced open cholecystectomy (OC) and is now widely used worldwide.<sup>[1,2]</sup> LC has become the gold standard in the surgical management of gallbladder diseases due to its well-established advantages, including reduced postoperative pain, quicker return to daily activities, and superior cosmetic outcomes.<sup>[3]</sup> Many of the factors previously considered absolute contraindications to LC have become relative with advances in surgical techniques and improved understanding of laparoscopic anatomy.

The most common indications for conversion from LC to OC are dense peritoneal adhesions and acute cholecystitis.<sup>[4,5]</sup> Additionally, the psychomotor skills and level

of surgical experience of the operating surgeon may also contribute to the likelihood of conversion.<sup>[6,7]</sup> Reported conversion rates in the literature range between 2% and 15%, and conversion is associated with prolonged hospitalization as well as increased morbidity and mortality.<sup>[8-10]</sup>

The risk of bile duct injury is higher during LC compared to OC. Previous studies report bile duct injury rates of 0.4–0.6% following LC and 0.1–0.2% following OC.<sup>[11,12]</sup> Although accumulated surgical experience and technological advances have reduced bile duct injury rates in LC over time, they still remain higher than those observed with OC.<sup>[13,14]</sup>

In this study, we aimed to identify the causes of conversion from LC to OC, describe the demographic characteristics of patients requiring conversion, and determine the conversion rate and associated risk factors.

## MATERIALS AND METHODS

The medical records of 74 patients who required conversion from laparoscopic cholecystectomy (LC) to open cholecystectomy (OC), out of a total of 4,165 patients who underwent cholecystectomy in the General Surgery Clinic of our hospital, were retrospectively reviewed. The study protocol was approved by the institutional ethics committee (Decision No: 2020/514/180/12; Date: 26/06/2020) and conducted according to the Declaration of Helsinki.

A total of 4,165 patients who underwent surgery between January 2016 and December 2021 were evaluated. The study included 74 patients who required conversion from LC to OC. Patients with symptomatic cholelithiasis, a history of previous abdominal surgery, those whose cholecystectomy was initiated laparoscopically, those who underwent LC following acute biliary pancreatitis, and those who underwent LC after endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis were eligible for inclusion. Acute cholecystitis was defined according to the Tokyo Guidelines 2018 (TG18). Surgeries performed at least three weeks after hospitalization for acute cholecystitis were considered elective cholecystectomies and were included.

Demographic characteristics, indications for conversion, conversion rate, intraoperative findings, and additional procedures performed during OC were recorded for patients who required conversion. Postoperative complications in patients who underwent OC were also documented. All patients underwent routine preoperative evaluation, including biochemical liver function tests and abdominal ultrasonography of the hepatobiliary system.

Patients who underwent emergency or early cholecystectomy (defined as cholecystectomy during the index admission for acute cholecystitis) were excluded. Additional exclusion criteria included hepatobiliary malignancy, gallbladder polyps, cholecystectomy performed concurrently with other abdominal procedures, prior upper abdominal

surgery requiring a primary open approach, inability to tolerate pneumoperitoneum, and elective cholecystectomies initiated as open procedures.

All LC procedures were performed by general surgeons in our clinic under general anesthesia, using a standard four-port technique, with pneumoperitoneum maintained at 12–14 mmHg.

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 24.0. Continuous variables such as age and length of hospital stay were analyzed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all variables. A p value of <0.05 was considered statistically significant.

## RESULTS

Of the 4165 patients who underwent cholecystectomy for symptomatic cholelithiasis, 74 (1.8%) were switched from LC to OC. Of the total 4165 LC, 2915 (70%) were female and 1250 (30%) were male. The conversion rate was determined as 1.8%. Of the patients who were switched from LC to OC, 33 (44.6%) were female and 41 (55.4%) were male. OC was passed in 33 (1.13%) cases out of 2915 LC in women and in 41 (3.28%) cases out of 1250 LC men. The mean age of all exposed patients was 56(40-82) years. While the average age of men was 60 (45-82) years, it was determined that women were 53 (40-76) years. The mean BMI was 30 (25-43) kg/m<sup>2</sup>. (Table 1)

Of the patients, 21 (28.3%) had hypertension, 16 (21.6%) had diabetes mellitus (DM), 7 (9.5%) had chronic obstructive pulmonary disease (COPD). Comorbidity was present in a total of 44 (59.4%) cases. It was determined that 3 (4.1%) patients had colon, 5 (6.75%) stomach, 1 (1.4%) small intestine and 4 (5.4%) gynecological operations. When the size of the stones was examined on USG, it was smaller than 1 cm (millimetric and multiple) in 51 (68.9%) patients, between 1-3 cm in 24 (32.9%) patients,

**Table 1.** Demographic characteristics of patients

	n (AC)	n (LC-OC)	% (Incidence)	p value
Total	4165	74	1.8	
Female	2915	33	1.13	<0.001
Male	1950	41	2.10	
Age (mean) (year, min-max)		56 (40-82)		<0.001
Female (year, min-max)		53 (40-76)		
Male (year, min-max)		60 (45-82)		
BMI (kg/m <sup>2</sup> ) (min-max)		30 (25-43)		=0.64 (NS)
Female (SD)		30.29±6.56		
Male (SD)		29.70±6.10		

min: Minimum; max: Maksimum; BMI: Body Mass Index; sd: standart deviation; AC: All Cholecystectomies; LC-OC: Conversion from Laparoscopic Cholecystectomy to Open Cholecystectomy; NS: non-significant.

**Table 2.** Preoperative risk factors and previous surgeries

Preoperative comorbidities	n (%)
HT	21 (28.3)
DM	16 (21.6)
COAH	7 (9.5)
Total	44 (59.4)
Previous surgeries	n (%)
Gastric	5 (6.75)
Gynecologic	4 (5.4)
Colon	3 (4.1)
Intestine	1 (1.4)
Total	13 (17.65)
Stone size (Usg)	n (%)
0-1 cm (multiple-mm)	51 (68.9)
1-3	24 (32.9)
Greater than 3 cm	9 (12.2)
Total	74 (100)
Additional pathologies	n (%)
ABP	6 (8.1)
ERCP	5 (6.75)
ERCP+ABP	2 (2.5)

HT: Hypertension; DM: Diabetes Mellitus; COAH: Chronic Obstructive Lung Disease; USG: Ultrasound; ABP: Acute Biliary Pancreatitis; ERCP: Endoskopik Retrograt Kolanjiyo Pankreatikografi.

and over 3 cm in 9 (12.2%) patients. It was determined that 5 (6.75%) of the patients underwent ERCP and 6 (8.1%) patients underwent ABP. Two (2.7%) of the patients had both ABP and ERCP. (Table 2)

The main reasons for conversion to open surgery in 74 cases are as follows. Adhesions or fibrosis due to previous surgery (n=41, 55.4%), cholelithiasis acute cholecystitis attack (n=19, 25.7%), inability to reveal anatomy due to adhesions in Calot's triangle (n=3, 4.1%), cystic artery or gallbladder bed were bleeding from the liver (n=4 5.4%), luminal organ damage (n=4, 5.4%), and biliary tract injury (n=3, 4.1%). (Table 3)

In the retrospective analysis of 74 cases, intraoperative complications were found in 11 (14.9%) patients. Bile duct injury in 3 (4.05%) cases, luminal organ injury in 4 (5.4%) cases, and bleeding from the cystic artery or gallbladder bed liver in 4 (5.4%) cases were detected. (Table 3)

As a postoperative complication; Bile leakage was observed in 3 (4.05%) cases, pulmonary complications in 3 (4.05%) cases, and surgical site infection in 2 (2.7%) cases. The cases with bile leakage were controlled with ERCP and stenting. The morbidity rate was 10.8% (8 cases), and none of the patients who developed complications required reoperation and were treated with conservative methods. There was no mortality in any of the patients in the postoperative period. (Table 4) The mean hospital stay was 2.2 (1-12) days.

**Table 3.** Conversion reasons and intraoperative complications

Reasons	n (%)
Adhesions due to previous surgeries or fibrosis	41 (55.4)
Acute cholecystitis attack	19 (25.7)
Luminal organ injury	4 (5.4)
Bleeding due to cystic artery or liver bed	4 (5.4)
Calot triangle abnormalities	3 (4.1)
Bile duct injury	3 (4.1)
Total	74 (100)
Intraoperative Complications	n (%)
Luminal organ injury	4 (5.4)
Bleeding due to cystic artery or liver bed	4 (5.4)
Bile duct injury	3 (4.1)
Total	11 (14.9)

**Table 4.** Postoperative complications

Complication	n (%)
Bile leak	3 (4.05)
Pulmonary complications	3 (4.05)
Surgical site infection	2 (2.7)
Total	8 (10.8)

## DISCUSSION

Laparoscopic cholecystectomy (LC) is widely accepted as the gold standard treatment for symptomatic gallstones.<sup>[15]</sup> As a minimally invasive technique, LC is preferred over open cholecystectomy (OC) worldwide, including in our country, due to its safety profile, reduced postoperative pain, faster recovery, and shorter hospital stay.<sup>[16]</sup> Nevertheless, conversion to OC remains necessary in certain clinical circumstances.<sup>[9,17]</sup> In our series of 4,165 patients operated for symptomatic gallstones over a five-year period, the conversion rate was 1.8%. Rosen et al.<sup>[18]</sup> reported a conversion rate of 5.3%, whereas a systematic review by Hu et al.<sup>[19]</sup> reported rates ranging from 1% to 15%.

Advanced age (>65 years) and male sex are recognized predictors of conversion. Sippey et al.<sup>[20]</sup> identified age as a significant risk factor. In a retrospective analysis by Genç et al.,<sup>[21]</sup> which included 5,164 LC cases, conversion rates were 2.25% in females and 5.65% in males (p<0.001), demonstrating a significant sex-based difference. Several studies have similarly reported that male sex and age over 50–65 years are associated with a two- to four-fold increased risk of conversion.<sup>[22-24]</sup> In our study, the mean age of converted patients was 56 years (40–82), and conversion was significantly more common in males. This may be attributable to the higher incidence of complicated cholecystitis and comorbidities among older patients.<sup>[25]</sup>

Recurrent episodes of acute cholecystitis can lead to gallbladder wall thickening, fibrosis, and adhesions, which may obscure anatomical landmarks and complicate dissection. Variations in biliary anatomy or increased adipose tissue in Calot's triangle may further contribute to operative difficulty. In our study, adhesions and bleeding in Calot's triangle were among the leading causes of conversion. Kaushik et al.<sup>[26]</sup> similarly reported that adhesions and common bile duct injuries were the most frequent indications for conversion. The reported rate of conversion due to intraoperative bleeding ranges from 0% to 1.9%, and Shurkalin et al.<sup>[27]</sup> recorded bleeding in 0.7% of patients, often related to vascular anatomical variations.

Kama et al.<sup>[9]</sup> identified male sex, previous upper abdominal surgery, gallbladder wall thickening, age >60 years, and acute cholecystitis as factors increasing the likelihood of conversion. Prior upper abdominal surgery is an important risk factor, as dense adhesions may hinder safe laparoscopic dissection. Akyürek et al.<sup>[28]</sup> reported significantly higher conversion rates in such patients. Consistent with these findings, previous abdominal surgery and related adhesions were notable contributors to conversion in our cohort.

Only a limited number of studies have assessed the effect of prior abdominal surgery and preoperative ERCP on conversion risk.<sup>[29-31]</sup> Karayiannakis et al.<sup>[29]</sup> demonstrated that prior upper abdominal surgery was associated with higher conversion rates and longer operative times due to the need for adhesiolysis. Sarli et al.<sup>[30]</sup> reported a conversion rate of 8.3% after ERCP compared with 3.4% in primary LC cases, while Ammori et al.<sup>[31]</sup> likewise suggested increased technical difficulty in patients with a history of ERCP.<sup>[30]</sup>

Intraoperative complications constitute another major indication for conversion. Historically, acceptable conversion rates for elective LC were reported as 3–5%; today, rates of 0–1% are reported in experienced centers. Bile duct injury rates during LC-to-OC conversion vary between 0% and 0.7%, compared to 0.2–1.4% for LC overall.<sup>[32-35]</sup> Although rare, prompt recognition and intraoperative repair offer the best outcomes. Hollow viscus injuries also occur during LC, with reported incidences up to 0.9%.<sup>[35]</sup> Careful pneumoperitoneum creation and meticulous use of electrocautery are essential in minimizing these risks. In our study, bile duct injury occurred in 3 patients (0.072%) and luminal organ injury in 4 patients (0.096%), consistent with published rates. Additionally, bile leakage was observed in 3 patients (4.1%) after conversion, all of which were successfully managed with ERCP.

Deizel et al.<sup>[36]</sup> reported intestinal perforation as a leading cause of mortality following laparoscopic procedures. Although intestinal perforation occurred in 4 patients (5.4%) in our study, no mortality was observed. Trocar- and Veress needle-related complications have also been described in the literature; major retroperitoneal vascular injuries occur in approximately 0.05% of cases and carry a mortality rate of 8.3%.<sup>[36]</sup>

Postoperative complications following conversion from LC to OC vary widely in the literature. Kaafarani et al.<sup>[37]</sup> reported wound infection, dehiscence, and deep vein thrombosis, whereas Ashfaq et al.<sup>[38]</sup> documented wound infection, postoperative bleeding, subhepatic collections, and bile leakage. In our study, postoperative complications—including wound infection, pulmonary complications, and bile leakage—were consistent with the morbidity patterns reported previously. Likewise, the observed length of hospital stay was similar to that described in other studies.

Our study has two notable strengths: First, it presents data from a high-volume single center; second, all procedures were performed by experienced surgeons with 20–25 years of laparoscopic expertise. However, the study has limitations. Its retrospective nature introduces inherent biases, and emergent cholecystectomies for acute cholecystitis were excluded because these procedures were performed in a separate emergency surgery unit. As a result, our conversion rate is among the lower rates reported in the literature.

## CONCLUSION

In conclusion, male sex, advanced age, and a history of previous upper abdominal surgery were identified as significant risk factors for conversion from LC to OC. Patients presenting with one or more of these factors should be informed preoperatively about the increased likelihood of conversion and should preferably be managed by experienced laparoscopic surgeons. Despite these considerations, LC remains the first-line surgical approach for symptomatic cholelithiasis. With increasing surgical experience and improvements in laparoscopic techniques, both conversion and complication rates are expected to further decline, even in high-risk patient groups.

### Ethics Committee Approval

Ethical approval for the study was granted by the Institutional Review Board of the Kartal Lütüf Kırdar City Hospital Clinical Research Ethics Committee (Date: 26.06.2020, Decision No: 2020/514/180/12).

### Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: A.B., H.F.K.; Design: A.B., M.F.B.; Supervision: G.C., A.B., M.T.; Fundings: A.B., M.T., H.F.K.; Materials: G.C., M.T.; Data: G.C., A.B., M.F.B.; Analysis: G.C., M.F.B.; Literature search: G.C., A.B., M.T.; Writer: G.C.; Critical Review: A.B., H.F.K.

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### Conflict of Interest

The authors declare no conflicts of interest.

## Presentation Statement

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## Laparoskopik Kolesistektomiden Açık Cerrahiye Dönüşün Nedenleri ve Risk Faktörlerinin Analizi

**Amaç:** Bu çalışma, laparoskopik kolesistektominin (LK) açık kolesistektomiye (AK) dönüş nedenlerini belirlemeyi ve dönüş oranı ile ilişkili demografik özellikleri ve risk faktörlerini değerlendirmeyi amaçlamaktadır.

**Gereç ve Yöntem:** Ocak 2016–Aralık 2021 tarihleri arasında kurumumuzda semptomatik kolelitiazis nedeniyle kolesistektomi yapılan toplam 4,165 hasta retrospektif olarak analiz edildi. LK'dan AK'ye dönüş gerektiren 74 hastada demografik özellikler, dönüş endikasyonları ve dönüş oranları değerlendirildi.

**Bulgular:** Çalışmaya dahil edilen 4,165 hastanın 74'ünde (%1.8) LK'dan AK'ye dönüş gerekti. Bu hastaların 33'ü (%44.6) kadın, 41'i (%55.4) erkekti. Ortalama yaş 56 (40–82) yıl, ortalama vücut kitle indeksi 30 (25–43) kg/m<sup>2</sup> idi. Hastaların 44'ünde (%59.4) komorbidite mevcuttu. Dönüşün başlıca nedenleri; önceki cerrahiye bağlı adezyon ve fibrozis (n=41, %55.4), akut kolesistit (n=19, %25.7), Calot üçgeninin net olarak ortaya konamaması (n=3, %4.1), sistik arter veya safra kesesi yatağı/karaciğerden kaynaklanan kanama (n=4, %5.4), lümen organ yaralanması (n=4, %5.4) ve biliyer trakt yaralanması (n=3, %4.1) olarak belirlendi. İntraoperatif komplikasyonlar 11 hastada (%14.9), postoperatif komplikasyonlar ise 8 hastada (%10.2) görüldü. Hiçbir hastada yeniden ameliyat gereksinimi ve mortalite saptanmadı. Ortalama hastanede kalış süresi 2.2 gündü (1–12).

**Sonuç:** LK, semptomatik safra taşı hastalığında tercih edilen cerrahi yaklaşım olmaya devam etmektedir. Bununla birlikte, belirgin risk faktörlerine sahip hastalarda işlemi ısrarla laparoskopik olarak tamamlama çabası morbiditeyi artırabilir. Uygun zamanda açık cerrahiye dönüş ve artan cerrahi deneyim komplikasyon oranlarının azaltılmasına katkı sağlayabilir.

**Anahtar Sözcükler:** Açık kolesistektomi; dönüş kolelitiazis; laparoskopik kolesistektomi.

# The Effect of Scleral Contact Lenses on Changes in Intraocular Pressure, Iridocorneal Angle, and Central Corneal Thickness

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**Keywords:** Anterior chamber; intraocular pressure; iridocorneal angle; scleral contact lens; Sirius corneal topography.



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## ABSTRACT

**Objective:** To investigate the impact of mini-Misa scleral contact lenses (SCLs, diameter: 16.5) on intraocular pressure (IOP), anterior chamber, and central corneal thickness (CCT)

**Methods:** Patients diagnosed with keratoconus who had been using SCL for at least 6 months were included. The anterior chamber angle (ACA), anterior chamber volume (ACV), anterior chamber depth (ACD), and CCT were evaluated with Sirius corneal topography [(Sirius CT), CSO, Italy] before and after 5 hours of SCL wear, with the lens in place. Additionally, IOP was measured using a pneumotonometer (Canon TX-20P; Tokyo, Japan) both before lens wear and immediately after removal.

**Results:** The SCL-corrected visual acuity was found to be 0.1 (0-1.3) LogMAR in twenty-four eyes of fourteen patients (4 females, 10 males), with a mean age of 37.9±10.4 years. After 5 hours of SCL wear, CCT values measured through the lens [478.5 (264-685) µm] were significantly higher than pre-wear values [417.0 (269-589) µm] (P<0.001). ACA [51 (38-68)° vs. 49 (38-66)°], ACD [3.74 (2.76-4.61) mm vs. 3.65 (2.57-4.25) mm], and ACV [210 (150-283) mm<sup>3</sup> vs. 196 (132-255) mm<sup>3</sup>] with SCL were also higher than pre-wear values (P=0.001, P<0.001, P<0.001, respectively). After 5 hours of SCL wear, K1 significantly decreased from 48.46 D (44.21-51.47) to 41.64 D (40.12-45.49), and K2 significantly decreased from 56.24 D (50.53-57.12) to 41.83 D (41.10-45.85) (P=0.001 for both). IOP was unchanged between the initial measurement and after removing the SCL [10 (6-20) mmHg vs. 11 (6-21) mmHg, respectively, P>0.05].

**Conclusion:** Besides not affecting IOP, SCLs were associated with an increase in CCT, ACA, ACD, and ACV after 5 hours of wear. These lenses do not appear to adversely affect IOP or narrow the iridocorneal angle.

## INTRODUCTION

Scleral contact lenses (SCL) have become increasingly popular in recent years for correcting refractive errors in conditions like keratoconus (KC), where the refractive errors are insufficient to be managed with standard refraction tests. SCLs are designed to rest on the conjunctival tissue over the sclera, creating a dome over the cornea and limbus. Unlike soft lenses, these SCLs settle on the conjunctival tissue over the sclera.<sup>[1,2]</sup>

Mini-SCLs (diameter: 14.0-16.5 mm) typically have narrower haptic wings and contact a relatively small area of the conjunctiva near the limbus, compared to larger SCLs.<sup>[3]</sup> Depending on the force applied and the concentration of the bearing surface on a smaller area near the limbus, they may compress structures responsible for aqueous humor outflow, such as Schlemm's canal, collector chan-

nels, or episcleral veins.<sup>[4]</sup> The compression of these structures can increase resistance to aqueous humor outflow, thereby raising intraocular pressure (IOP).

Previous studies have demonstrated the effects of SCL use on central corneal thickness (CCT), K-values, and IOP.<sup>[5-7]</sup> However, we have not found a study in the literature that measures the effect of SCL use on the iridocorneal angle using Scheimpflug Sirius Corneal Topography [(Sirius CT), CSO, Italy], except for one study in which optical coherence tomography (OCT) was used.<sup>[8]</sup>

We aim to investigate whether there are any differences in IOP, CCT measured by Sirius CT, iridocorneal angle, and other anterior chamber parameters with the application of SCLs in patients who use them clinically, and to evaluate the relationship between these parameters.

## MATERIALS AND METHODS

### Patients and Study Design

Patients who were diagnosed with KC and were using 16.5 mm mini-Misa SCL Microlens Contact Lens Technology, Arnhem, Netherlands) at our hospital, department of ophthalmology, contact lens unit between August 1, 2020, and June 1, 2024, were included in the study. Only patients who had been using SCL regularly for at least 6 months and had maintained consistent follow-up visits were considered. At the time of enrollment, all participants were clinically verified to have an appropriate lens fit, with no signs of poor fitting such as excessive blanching, inadequate vault, discomfort, or decentration. The patients who underwent Sirius CT examinations both before SCL fitting and after 5 hrs of lens wear were included in the study. According to the mini-Misa SCL guideline and our experience, lens wear beyond 5 hrs is not recommended to prevent a possible decrease in the vault. Therefore, all Sirius CT measurements were obtained on the same day—during SCL fitting and after 5 hrs of lens wear—taken with the lens still in place immediately before removal.

Patients 18 years of age or older with a history of ocular surgery other than corneal cross-linking were excluded from the study. This exclusion also applied to individuals who had undergone any form of keratoplasty. Additionally, patients with chronic eyelid disease, keratitis, active or previous uveitis, congenital cataract, congenital retinal dystrophies, ocular trauma, any systemic disease (including cardiovascular, metabolic, hematologic, or other disorders), or a genetic syndrome were excluded. Only eyes with an axial length between 22 and 25 mm were included.

The detailed ophthalmological examination findings, including autorefractive measurements, SCL-corrected visual acuity using the Snellen chart (converted to LogMAR), and anterior and posterior segment examinations were performed. IOP measurements with a pneumotonometer (Canon TX-20P; Tokyo, Japan) were taken both before SCL fitting, between 8:00 a.m. and 10:00 a.m. to avoid diurnal fluctuations, and immediately after lens removal. The flat K (K1) and steep K (K2) values in the central 3-mm area, anterior chamber angle (ACA), anterior chamber volume (ACV), anterior chamber depth (ACD), and CCT from the Sirius CT examinations were recorded.

Patients with any eye condition other than KC that could impair visual acuity, those with Sirius CT scans of insufficient image quality, and those with incomplete examination history data in the system, resulting in insufficient data for the study, will be excluded from the study.

### Scheimpflug Imaging

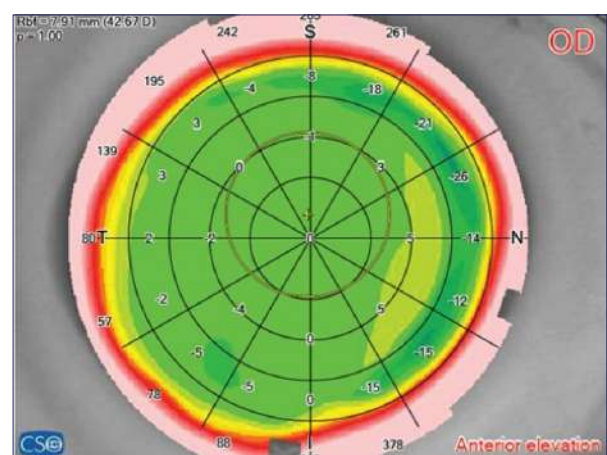
The Sirius Scheimpflug analyzer combines a Placido disc with a mono-rotating Scheimpflug system for corneal photography. It captures up to 100 high-resolution corneal sections to calculate all biometric measurements of the anterior chamber. The high measurement speed minimizes

the effect of eye movement, ensuring high-quality and accurate results. The device provides detailed information on both the anterior and posterior surfaces of the cornea. In two seconds, it acquires approximately 25 Scheimpflug scan images.<sup>[9,10]</sup>

To ensure optimal image quality, three well-focused, aligned, and centered images were captured for each eye using the Sirius CT (CSO, Florence, Italy). Patients were asked to blink before each acquisition to minimize the effect of tear film irregularities. K1, K2, Kmax in the central 3-mm area, ACA, ACD, ACV, and CCT were automatically measured by the device. ACA was defined as the angle between the posterior corneal surface and the anterior iris surface, measured 500  $\mu$ m from the scleral spur in six meridians (6–12, 1–7, 2–8, 3–9, 4–10, and 5–11 o'clock), and the mean value from 12 points was calculated (Fig. 1). ACD was defined as the distance from the corneal endothelium to the anterior lens surface, ACV as the total volume of the AC bounded by the corneal endothelium and the anterior lens surface, and CCT as the thinnest corneal point determined by the pachymetric map.

### Statistical Analysis

The sample size was calculated using G\*Power 3.1.9.6 (Heinrich Heine University, Düsseldorf, Germany) with a power of 0.8 and an  $\alpha$  error of 0.05. For the statistical analysis, IBM SPSS Statistics version 24 (NY, USA) was utilized. To determine if the data followed a normal distribution, the Shapiro-Wilk test was conducted. The Wilcoxon Signed Rank Test was applied to compare the differences between the pre-SCL wearing levels and measurements taken through the lens after 5 hrs of wear. Furthermore, the Spearman correlation test was used to evaluate the correlation between pre-SCL and post-SCL changes in IOP and the anterior chamber values.  $P < 0.05$  was considered the significance level.



**Figure 1.** Six cross-sectional meridians with twelve points where anterior chamber angle measurements were performed.

**Table 1.** Characteristics of eyes included in the study

Patients (female/male)	14 (4/10)
Eyes (right / left)	24 (12/12)
Age (years)*	37.9±10.4
Duration of SCL use (month)*	28.4±22.9 (6-72)
K max (D)†	56.8 (46.58-72.67)

D: Diopter; K max K maximum; SCL: Scleral contact lens.  
\*Mean±standard deviation. †Median (minimum-maximum).

## The Ethics Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants. Ethical approval was granted by Kartal Dr. Lütfi Kırdar City Hospital's scientific research ethics committee under the reference number 2024/010.99/6/6 and date: 26/07/2024.

## RESULTS

Twenty-four eyes (12 right, 12 left) from fourteen patients (4 females, 10 males) diagnosed with KC, with a mean age of 37.9±10.4 years, were included in our study. The duration of SCL use was 28.4±22.9 months (Table 1). The SCL-corrected visual acuity in eyes using SCL significantly improved after 5 hrs of lens wear, increasing from 0.7 (0.2–1.6) LogMAR before wear to 0.1 (0–1.3) LogMAR while wearing them (P<0.001).

A significant increase was observed in the ACA [49 (38–66) vs. 51 (38–68)°], ACD [3.65 (2.57–4.25) mm vs. 3.74 (2.76–4.61) mm], ACV [196 (132–255) mm<sup>3</sup> vs. 210 (150–283) mm<sup>3</sup>], and CCT [417.0 (269–589) µm vs. 478.5 (264–685) µm] values of the eyes included in the study after SCL use compared to before (P=0.001, P<0.001, P<0.001, P<0.001; respectively). Conversely, a significant decrease was noted in K1 [48.46 D (44.21–51.47) vs. 41.64 D (40.12–45.49)] and K2 [56.24 D (50.53–57.12) vs. 41.83 D (41.10–45.85)] values with lens use (both P=0.001). No significant dif-

ferences were observed in IOP levels between measurements taken initially and after SCL removal [10 (6–20) mmHg vs. 11 (6–21) mmHg, respectively, P>0.05] (Table 2). No significant correlations were found between pre- and post-SCL changes in IOP and anterior chamber values (all P>0.05).

## DISCUSSION

This study demonstrated an increase in ACA, ACD, and ACV, as assessed by Sirius CT, in individuals who had been wearing SCL for at least 6 months, observed after 5 hrs of lens wear. Additionally, an increase in CCT values measured by Sirius CT over the lens was noted, along with a decrease in K1 and K2 values. However, no effect of SCL wearing on IOP was observed.

A study showed that mini SCLs were found to improve visual acuity and vision-related quality of life as measured by the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-39) in eyes with KC.<sup>[11]</sup> Another study also found similar results in eyes with KC, pellucid marginal degeneration, and post-keratoplasty astigmatism.<sup>[12]</sup> In our research, a significant improvement in SCL-corrected visual acuity was observed in eyes fitted with SCL, consistent with findings reported in the literature.

Many studies have explored the impact of SCL use on IOP. A study found that wearing a small-diameter (15 mm) SCL for 2 hrs led to no significant difference in IOP, as measured by corneal and scleral pneumotometry.<sup>[3]</sup> A small minority of subjects exhibited an increase in IOP, which was thought to be possibly attributable to tight lens fittings, narrow ACA, and impaired aqueous humor drainage. However, another study reports that properly fitted modern SCLs do not significantly raise IOP in the short term, even though they primarily cause superficial compression of tissue near the scleral spur following 3 hrs of lens wear.<sup>[13]</sup> In another research study, a decrease in IOP was observed after 3 to 8 hrs of SCL wear, as measured by an air-puff tonometer.<sup>[14]</sup> However, depending on the efficiency of aqueous humor drainage, increased IOP

**Table 2.** Measurement changes associated with scleral contact lens wear†

	Pre-SCL	Post-SCL	P*
SCL-CVA (LogMAR)	0.7 (0.2-1.6)	0.1 (0-1.3)	<0.001
IOP (mm Hg)	10 (6–20)	11 (6–21)	>0.05
ACA (°)	49 (38-66)	51 (38-68)	0.001
ACD (mm)	3.65 (2.57-4.25)	3.74 (2.76-4.61)	<0.001
ACV (mm <sup>3</sup> )	196 (132-255)	210 (150-283)	<0.001
CCT (µm)	417.0 (269-589)	478.5 (264-685)	<0.001
K1 (D)	48.46 D (44.21-51.47)	41.64 D (40.12-45.49)	0.001
K2 (D)	56.24 D (50.53–57.12)	41.83 (41.10-45.85)	0.001

ACA: Anterior chamber angle; ACD: Anterior chamber depth; ACV: Anterior chamber volume; CCT: Central corneal thickness; IOP: Intraocular pressure; SCL: Scleral contact lens; SCL-CVA SCL corrected visual acuity. \*Wilcoxon Signed Rank Test. †Median (minimum-maximum).

during lens wear might stimulate aqueous humor outflow, which could clarify the lower IOP observed after taking off the lenses. Techniques such as the Honan balloon<sup>[15]</sup> and ocular massage before cataract surgery<sup>[16]</sup> show how elevated IOP can be decreased by improving aqueous humor outflow over time. This theory suggests that the effectiveness of aqueous outflow and the degree of IOP elevation during lens use influence the IOP measured after lens removal, thereby explaining why subjects with a normal outflow capacity, unaffected by the lens, may exhibit lower IOP readings.

It has been thought that the increase in IOP might be more pronounced with smaller-diameter lenses and a reduction in the scleral areas, leading to narrower haptic zones.<sup>[3]</sup> Accordingly, a larger lens would distribute contact more broadly across the ocular surface, causing less indentation on the ocular surface. However, a study suggested that SCLs can cause a statistically significant increase of approximately 5 mm Hg in mean IOP after 4 hrs of wear, regardless of lens diameter, in eyes fitted with either a 15.8 mm or 18 mm lens, using transpalpebral Diaton tonometry,<sup>[17]</sup> which is known for its lower concordance with the gold standard, Goldmann tonometry.<sup>[18]</sup> Additionally, Fogt et al.<sup>[19]</sup> investigated how a 15.2 mm and an 18.0 mm SCL diameter affect IOP over 1 hour of lens wear. They measured IOP using both pneumotonometry and transpalpebral tonometry. While pneumotonometry showed no significant change in mean IOP compared to baseline, transpalpebral tonometry revealed a significant difference. In a recent study, the IOP measurements taken from the cornea using pneumotonometry were consistent with baseline levels, showing no significant difference in healthy individuals during 5 hrs of lens wear, and this situation was independent of lens diameter.<sup>[20]</sup> In our study, eyes were treated with 16.5 mm mini-Misa SCL. Consistent with the current research, we measured IOP from the cornea using non-contact pneumotonometry before and after the removal of the SCL, following 5 hrs of wear, and found no significant change in IOP. In addition, IOP correction for CCT tends to underestimate IOP in thin corneas and overestimate it in thick corneas when measured by Goldmann applanation tonometry; however, these corrections are valid only for corneas with intact biomechanics. In eyes with biomechanically compromised thin corneas, such as in keratoconus, IOP measurements may be inaccurate. Furthermore, in edematous corneas that can develop after SCL wear, thick cornea corrections may paradoxically lead to underestimation of IOP.<sup>[21,22]</sup> Therefore, no CCT-based correction was applied in this study, particularly because non-contact tonometry was used.

Additionally, some reports found a statistically significant increase in CCT measured by Pentacam after 8 hrs ( $P=0.001$ )<sup>[6]</sup> and 6 hrs of lens wear before lens removal ( $P=0.06$ ).<sup>[7]</sup> Another study showed no significant difference in CCT values or IOP after SCL wear in eyes with KC or PK measured using the Scheimpflug imaging (CORVIS ST).<sup>[23]</sup> In our current report, we performed Sirius CT while

the SCLs were on the eyes with KC and found a statistically significant increase in CCT ( $P=0.001$ ).

In addition, the mean K1, K2, and Kmax values were found to be significantly lower after lens removal compared to those  $\geq 1$  week after SCL removal using Pentacam in keratoconus patients ( $P=0.037$ ,  $P<0.001$  vs.  $P<0.001$ , respectively).<sup>[24]</sup> A different study demonstrated anterior corneal curvature flattening in keratoconus eyes following 8 hrs of SCL wear.<sup>[25]</sup> Although statistically insignificant, another study also reported a reduction in K1, K2, and Kmax values after 6 hrs of scleral lens wear in eyes with keratoconus.<sup>[7]</sup> In our study, a flattening of K values measured through SCL was observed in keratoconus eyes at the end of 5 hrs, consistent with previous studies ( $P<0.05$ ).

Besides, the only available study examining anterior chamber parameters in patients using SCL reported a statistically insignificant increase in ACA values, measured by OCT, 10 minutes after lens removal following 4 hrs of wear;<sup>[8]</sup> however, it did not include details regarding the measurement process. In the users of mini-SCLs, the pressure exerted and the concentration of force on a smaller area near the limbus can potentially compress structures, including Schlemm's canal, collector channels, or episcleral veins. However, in the current study, no negative effect on IOP was observed when an optimized fitted SCL was used ( $P>0.05$ ). The narrower haptics apply pressure to a small area near the limbus, which may result in perilimbal centripetal compression, leading to an increase in ACA, ACD, and ACV without affecting IOP. In addition, the increases in ACA, ACD, and ACV observed with SCL wear likely reflect the mechanical influence of the lens on corneal curvature and anterior segment morphology. Despite these geometric changes, the absence of any significant alteration in IOP suggests that trabecular outflow dynamics remain largely unaffected. These findings indicate that while short-term SCL use induces measurable anatomical expansion of the anterior segment, it does not appear to pose a clinically relevant risk in terms of IOP. To better assess the impact of SCLs on anterior chamber parameters and IOP, studies comparing different SCL diameters would be beneficial.

Mini-SCLs vault over the cornea and rest on the conjunctiva and sclera, thereby surrounding the limbus without directly contacting the corneal surface. The limbus, forming a ring approximately 1.5–2 mm wide around the cornea, contains the corneal endothelium, scleral vessels, and the initial portion of the trabecular meshwork. Schlemm's canal, located immediately on the scleral side of the limbus, serves as the main pathway for aqueous humor drainage from the anterior chamber into the venous system, with episcleral veins receiving the outflow.<sup>[26,27]</sup> Functionally, mini-SCLs may exert slight pressure on the episcleral veins and lymphatics; however, if properly fitted, venous and lymphatic circulation is generally preserved, and Schlemm's canal and aqueous humor outflow remain typically unaffected.

It is promising that well-fitted SCLs may not cause clinically significant increases in IOP. However, any IOP ele-

vation induced by SCL may still have pathological consequences, particularly in patients with glaucoma and those who wear their lenses regularly and for extended periods. This susceptibility is likely to be higher in patients with thin corneas, such as those with KC.

This study has several limitations, including the lack of access to the cornea and the inability to directly measure corneal IOP while wearing SCL, so we had to rely on IOP measurements taken immediately after lens removal. Additionally, our sample was not evenly distributed between males and females, and the findings of this study may only apply to young patients diagnosed with KC. Since our study included individuals who have been using lenses for an average of approximately 28 months, it may provide an advantage in demonstrating the long-term effects of SCL on IOP. However, although baseline ACA measurements prior to lens wear were available, no longitudinal follow-up was performed. Therefore, evaluating the glaucomatous effect of SCLs based on a single measurement is challenging, which should be acknowledged as another study limitation.

These lenses do not seem to adversely affect IOP or aqueous outflow by narrowing the iridocorneal angle. Studies with an increased number of patients, ensuring a homogeneous age range and gender distribution, including individuals predisposed to glaucoma, as well as the use of lenses with different diameters, will be beneficial.

#### Ethics Committee Approval

The study was approved by the Kartal Dr. Lutfi Kırdar City Hospital Scientific Research Ethics Committee (Date: 26.07.2024, Decision No: 2024/010.99/6/6 and 26/07/2024).

#### Informed Consent

Written informed consent was obtained from all participants.

#### Peer-review

Externally peer-reviewed.

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#### Statements and Declarations

This study was partly presented at the 58th National Congress of the Turkish Ophthalmological Association (TOA), during the TOA-Young Ophthalmologist panel, held in Antalya, Türkiye, from November 20 to 24, 2024.

#### Authorship Contributions

Concept: F.I.S.D., A.P.; Design: F.I.S.D., A.P.; Supervision: A.P.; Data collection &/or processing: F.I.S.D., A.P.; Analysis and/or interpretation: F.I.S.D., A.P.; Literature search: F.I.S.D., A.P.; Writing: F.I.S.D.; Critical review: F.I.S.D., A.P.

#### Conflict of Interest

None declared.

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### Skleral Kontakt Lenslerin Göz İçi Basıncı, İridokorneal Açığı ve Santral Kornea Kalınlığı Üzerindeki Etkisi

**Amaç:** Bu çalışmada, mini-Misa skleral kontakt lenslerin (SKL, çap: 16.5) göz içi basıncı (GİB), ön kamara ve santral kornea kalınlığı (SKK) üzerindeki etkileri araştırılmıştır.

**Gereç ve Yöntem:** En az 6 aydır SKL kullanan keratokonus tanılı hastalar çalışmaya dahil edildi. SKL takılmadan önce ve takıldıktan 5 saat (saat) sonra, lens gözdeyken; ön kamara açısı (ÖKA), ön kamara hacmi (ÖKH), ön kamara derinliği (ÖKD) ve SKK, Sirius kornea topografi cihazı [(Sirius CT), CSO, İtalya] ile değerlendirildi. Ayrıca, GİB ölçümleri lens takılmadan önce ve lens çıkarıldıktan hemen sonra, bir pnömotonometre (Canon TX-20P; Tokyo, Japonya) ile yapıldı.

**Bulgular:** On dört hastaya (4 kadın, 10 erkek) ait yirmi dört gözde, SKL ile düzeltilmiş görme keskinliği 0.1 (0-1.3) LogMAR bulundu. 5 saatlik SKL kullanımının ardından, lens üzerinden ölçülen SKK değerleri [478.5 (264-685) µm], öncesindeki değerlere göre [417.0 (269-589) µm] anlamlı şekilde daha yüksek bulundu (P<0.001). Lens takılıken ölçülen ÖKA [51 (38-68)° ve 49 (38-66)°], ÖKD [3.74 (2.76-4.61) mm ve 3.65 (2.57-4.25) mm] ve ÖKH [210 (150-283) mm<sup>3</sup> ve 196 (132-255) mm<sup>3</sup>] değerleri de, lens öncesi değerlerden anlamlı olarak daha yüksek bulundu (sırasıyla, P=0.001, P<0.001, P<0.001). SCL kullanımından 5 saat sonra, K1 [48.46 D (44.21–51.47) ve 41.64 D (40.12–45.49); P=0.001] ve K2 [56.24 D (50.53–57.12) ve 41.83 D (41.10–45.85); P=0.001] anlamlı şekilde azaldı. GİB, başlangıç ölçümü ile lens çıkarımı sonrası ölçüm arasında değişiklik göstermedi [10 (6–20) mmHg ve 11 (6–21) mmHg, P>0.05].

**Sonuç:** SKL'ler GİB üzerinde anlamlı bir değişiklik oluşturmazken; 5 saatlik kullanım sonrası SKK, ÖKA, ÖKD ve ÖKH'de artışa neden olmuştur. Bu lensler GİB'i olumsuz etkilememekte ve iridokorneal açının daralmasına yol açmamaktadır.

**Anahtar Sözcükler:** Göz içi basıncı; iridokorneal açığı; ön kamara; Sirius korneal topografisi; skleral kontakt lens.

# Validity and Reliability of the Turkish Version of Balance Outcome Measure for Elder Rehabilitation

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**Keywords:** Balance; Berg Balance Scale; elderly; reliability; validity.



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## ABSTRACT

**Objective:** This study aimed to determine validity and reliability of the Turkish version of Balance Outcome Measure for Elderly Rehabilitation (BOOMER) and to evaluate its psychometric properties.

**Methods:** The study included 60 elderly individuals (30 women, 30 men; mean age  $72.03 \pm 7.86$  years). Participants completed the four subtests of the BOOMER (Step Test, Timed Up and Go Test, Functional Reach Test, Timed Static Stand Test) and the Berg Balance Scale (BBS). Descriptive statistics were calculated, Cronbach's alpha and Kendall's W coefficient were used for internal consistency, and Spearman's correlation was used to examine item-total relationships and correlations between the BOOMER and the BBS.

**Results:** The total BOOMER score was found to be  $12.52 \pm 0.95$ . Significant correlations were observed between the subtests and the total BOOMER score ( $r=0.414-0.565$ ,  $p<0.01$ ). The Cronbach's alpha coefficient was low at 0.022, but the Kendall W coefficient showed moderate reliability at 0.339. For the BBS, the alpha was initially 0.304, but it increased to 0.548 after item-total correlation analysis. A positive and significant correlation was found between the BOOMER total score and the BBS total score ( $r=0.419$ ,  $p=0.001$ ).

**Conclusion:** The BOOMER scale is a practical measure that can assess static, dynamic, and functional balance in older adults in a short time. Its significant correlation with the BBS supports the concurrent validity of the scale. However, considering the low internal consistency values, it is recommended that reliability findings be strengthened through further studies in different populations and with larger samples.

## INTRODUCTION

Balance problems are common in older adults and are usually caused by factors such as muscle weakness, chronic diseases, side effects of medications, and disorders of the vestibular and somatosensory systems.<sup>[1,2]</sup> The aging process leads to changes in the body's center of gravity and deterioration in posture alignment. Thus, this requires a wider support surface and negatively affects balance. Additionally, secondary issues such as fear of falling can limit daily living activities.<sup>[3]</sup>

Balance is achieved through the integration of information from the somatosensory, vestibular, and visual systems by the central nervous system.<sup>[4]</sup> While the somatosensory system transmits proprioceptive data from muscles and joints, the vestibular system regulates head movements, body alignment, and head-eye coordination. In addition, the visual system supports postural control with environmen-

tal cues. Therefore, decreased visual acuity can directly negatively affect balance.<sup>[5]</sup>

The central nervous system maintains balance by activating muscles using specific strategies.<sup>[6]</sup> In mild postural disturbances, the ankle strategy is used, and muscles contract from distal to proximal. However, with aging, this process slows down, and proximal muscles engage earlier.<sup>[7]</sup> In more severe imbalances, the hip strategy or step strategy is applied.<sup>[8]</sup> Young individuals maintain balance with a single large step, while older individuals often have to take many small steps.<sup>[8]</sup>

Balance measurements can be unidimensional or multidimensional. Unidimensional tests (e.g., Step Test, Functional Reach Test) assess a specific aspect of postural control and are quick to administer.<sup>[9]</sup> Multidimensional tests are more comprehensive; the Berg Balance Scale (BBS) is an example.<sup>[10]</sup> However, the validity of these tests in different

rehabilitation settings for older adults may be limited.<sup>[11]</sup> In clinical practice, using comprehensive yet simple measurements together yields more accurate results.<sup>[12]</sup> While comprehensive tests such as the BBS are considered the gold standard, their lengthy administration time can lead to limitations in clinical practice.<sup>[12]</sup> The Balance Outcome Measure for the Elder Rehabilitation (BOOMER), developed in response to this need, combines short and practical subtests such as the Step Test, Timed Up and Go Test, Functional Reach Test, and Timed Static Stand Test to comprehensively assess static, dynamic, and functional balance in older adults.<sup>[13]</sup> Therefore, this study aimed to determine validity and reliability of the Turkish version of balance outcome measure for elder rehabilitation scale, and evaluate its psychometric properties.

## MATERIALS AND METHODS

### Procedures

This study was conducted between November 2022 and January 2023. Ethical approval was obtained from the Human Research Ethics Board of Marmara University (No: 48, Date: 30/03/2023) and conducted according to the Declaration of Helsinki. Verbal and written explanations were provided to participants about the study, and all participants provided written informed consent. This study was registered on ClinicalTrials.gov with registration number NCT07129213.

### Subjects

This research was carried out on sixty (n=60) healthy elderly participants who were aged between 60-88 years. None of the participants used any assistive devices such as a cane or walker. Essential information for inclusion and exclusion criteria using a socio-demographic questionnaire. Inclusion criteria included individuals who can read and write Turkish, have a Mini Mental State Examination score of 24 or higher, and have no visual or auditory pathology. Exclusion criteria included individuals who had undergone amputation or have walking problems such as paraplegia or tetraplegia, have Alzheimer's disease and dementia, and were unable to follow the commands necessary for the study. Besides, individuals who declined to participate in the study were excluded.

Since this research was a cross-sectional survey, the researchers employed several tests, including the BOOMER and the BBS test, to collect essential data for the study.

### The BOOMER consists of the following tests:

**Step Test (ST):** The Step Test required weight shifting and movement while in a single-leg stance, in addition to controlling motor activity of the lower extremities. The number of repetitions of placing one foot onto a 7.5-cm step and returning it to the ground within 15 seconds was recorded. Scores were calculated based on the average of both legs. If the participant could not perform the test, it was regarded as grade 0; 0–5 repetitions were grade 1, 5–8 repetitions grade 2, 8–12 repetitions grade 3, and >12

repetitions were considered grade 4.

**Timed Up and Go (TUG) Test:** This screening test measured the likelihood of falling in older adults. The participant stood up, walked 3 meters, turned 180 degrees, walked back, and sat down with their back against the chair. The completion time (in seconds) was recorded. If the participant was unable to perform the task, it was graded 0;  $\geq 30$  s was grade 1, 29–20 s grade 2, 19–10 s grade 3, and  $< 10$  s was regarded as grade 4.

**Functional Reach Test (FRT):** This test assessed dynamic balance by measuring the distance reached with an outstretched arm while maintaining a fixed base of support. The distance between the starting point and the maximal forward reach was recorded in centimeters. If the participant could not perform the test, it was graded 0; 1–15 cm was grade 1, 16–20 cm grade 2, 21–30 cm grade 3, and  $> 30$  cm was grade 4.

**Timed Static Stand (TSS) Test:** This screening test involved observing participants standing with their feet together and eyes closed, thereby narrowing their base of support. Time (in seconds) was recorded until balance was lost. If balance was lost immediately, the score was 0;  $< 30$  s was grade 1, 30–60 s grade 2, 60– $< 90$  s grade 3, and  $\geq 90$  s was grade 4.

The overall BOOMER score was calculated by summing the item scores, yielding a total score between 0 and 16. Higher scores indicated better balance ability and a lower risk of falling.<sup>[12]</sup>

**Berg Balance Scale:** The BBS was used as an objective method to assess balance. Participants were asked to perform predetermined tasks to determine whether they could maintain balance safely. The questionnaire consisted of 14 items, each rated from 0 to 4, with 0 representing the lowest level of function and 4 representing the highest. The test required approximately 20 minutes to complete. Most items required the participant to maintain a specific position for a defined period. When a participant did not meet the required time or distance, when supervision was needed, when external support was touched, or when assistance was provided by the examiner, points were progressively deducted. The total score ranged from 0 to 56. Since the BBS had previously been confirmed as a valid indicator of balance performance, we used it to determine the reliability of the BOOMER balance outcome measure.<sup>[14,15]</sup>

### Statistical Analysis

The sample number of the study was calculated with the program named G\*Power 3.1.9.2. The sample size of the study was calculated as 60 in total, with an error of  $\pm 0.5$ , an effect size of 0.44 calculated for the estimated standard deviation of 1.26, a power of 95%, and a margin of error of 5% for Type I. The sample size of the study was calculated by power analysis based on the effect size of previously published similar studies.<sup>[13]</sup>

Data analysis will be done using the SPSS-26 statistical package program. In the analysis of socio-demographic

**Table 1.** Demographic characteristics of the individuals

Characteristics (n=60)	Mean (SD)
Age (years)	72.0 (7.9)
Height (cm)	169.4 (9.1)
Weight (kg)	74.5 (9.5)
BMI, kg/m <sup>2</sup>	26.2 (4.8)
Gender (n) (%)	
Female	30 (50%)
Male	30 (50%)

SD: Standard deviation; BMI: Body mass index.

data, descriptive statistics such as percentage, frequency, median, minimum-maximum values, mean and standard deviation will be used. To determine the content validity of the scale, analyses related to content validity ratio and content validity index values will be completed. Principal component analysis was used in explanatory factor analysis. Bartlett Sphericity test and Keiser-Mayer-Olkin tests was used to determine the adequacy of the scale content and sample size. The factor structure and factor load of the scale was examined with confirmatory factor analysis. Spearman's rank correlation coefficient was preferred for item-total analyses because the BOOMER items are ordinal (0–4 scoring) and the data did not meet normality assumptions.

## RESULTS

A total of 60 elderly individuals (30 women, 30 men) were

The total BBS score was found to be  $43.25 \pm 2.10$  on average. In the analysis conducted within the scope of convergent validity, a significant and positive correlation was found between the BOOMER total score and the BBS total score ( $r=0.419$ ;  $p=0.001$ ). Furthermore, each of the BOOMER items was significantly correlated with the BBS total score ( $r=0.414-0.565$ ;  $p<0.01$ ) (Table 2).

### Item-Total Correlations

The relationship between the BOOMER scale item scores and the total score was evaluated using Spearman correlation analysis. ST ( $r=0.565$ ;  $p<0.001$ ), TUG test ( $r=0.414$ ;  $p=0.001$ ), TSS test ( $r=0.523$ ;  $p<0.001$ ), and FRT ( $r=0.492$ ;  $p<0.001$ ) each showed a significant and positive correlation with the total score. These findings supported that the BOOMER scale's items contributed to the scale as a whole and had internal consistency (Table 3).

### Reliability Analyses

The Cronbach's alpha coefficient for the BOOMER scale was found to be 0.022. The presence of only four subtests in the scale may have contributed to this low alpha value. The nonparametric fit index Kendall's correlation coefficient W was calculated as 0.339, indicating a moderate level of reliability. Furthermore, Spearman correlation analysis revealed that each item was significantly correlated with the total score ( $p<0.05$ ). These results indicated that BOOMER had limited internal consistency.

The initial Cronbach's alpha coefficient for the BBS was 0.304. When items with low item-total correlations were removed, this value increased to 0.548. According to the

**Table 2.** Correlations between the mean values of the BOOMER scale's items, total score and the Berg Balance Scale

BOOMER Items	Mean $\pm$ SD	Correlation with BBS (r)	p
Step Test	3.40 $\pm$ 0.49	0.565	<0.001
Timed Up and Go Test	3.20 $\pm$ 0.40	0.414	0.001
Timed Static Stand Test	3.28 $\pm$ 0.45	0.523	<0.001
Functional Reach Test	2.63 $\pm$ 0.52	0.492	<0.001
BOOMER Total	12.52 $\pm$ 0.95	0.419	0.001

BOOMER, Balance Outcome Measure for the Elder Rehabilitation; Correlation is significant at the 0.01 level (2-tailed).

included in the study. Descriptive statistics regarding the demographic characteristics of the participants were presented in Table 1.

### BOOMER Scale Results and Their Relationship with BBS

The mean scores obtained from the BOOMER scale items were  $3.40 \pm 0.49$  for the ST,  $3.20 \pm 0.40$  for the TUG test,  $3.28 \pm 0.45$  for the TSS test, and  $2.63 \pm 0.52$  for the FRT. The total BOOMER score was calculated as  $12.52 \pm 0.95$  (Table 2).

**Table 3.** Correlations between BOOMER item scores and total scores

BOOMER Items	Item-Correlation (r)	p
Step Test	0.565	<0.001
Timed Up and Go Test	0.414	0.001
Timed Static Stand Test	0.523	<0.001
Functional Reach Test	0.492	<0.001

BOOMER: Balance Outcome Measure for the Elder Rehabilitation; Correlation is significant at the 0.01 level (2-tailed).

exploratory factor analysis, three factors were identified, highlighting distinct aspects of balance.

### Construct Validity

In the exploratory factor analysis conducted on the BBS, the Kaiser–Meyer–Olkin (KMO) value was 0.430, and Bartlett's sphericity test was found to be close to the significance level ( $\chi^2=111.5$ ;  $df=91$ ;  $p=0.071$ ). Three factors with eigenvalues above 1 were extracted, explaining 37.6% of the total variance. Following Varimax rotation, different items were grouped under these three factors.

## DISCUSSION

This study aimed to examine the validity and reliability of the Turkish version of the Balance Outcome Measure for Elder Rehabilitation. In this context, the psychometric properties of the scale were evaluated and comparative analyses were conducted with an established balance assessment tool. The findings indicated that the BOOMER may be a valid and reliable measure for assessing static, dynamic, and functional balance in older adults.<sup>[12,13]</sup>

The subscales of the BOOMER scale (ST, TUG test, FRT, and TSS test) showed significant correlations individually. This finding supports that each subscale contributes to the total BOOMER score and that the scale provides a comprehensive assessment.<sup>[13]</sup> However, the low Cronbach's alpha coefficient may be due to the limited number of items and the different dimensions measured by the tests. Therefore, although internal consistency is limited, Spearman correlation analyses support the internal validity of BOOMER. Furthermore, the extremely low Cronbach's alpha coefficient (0.022) may also be attributed to the limited number of items in the BOOMER scale. Short scales with few items frequently produce low alpha values, even when items measure related constructs; thus, Cronbach's alpha may underestimate the true reliability of the instrument.<sup>[14]</sup>

The BBS is a widely used measure in balance assessments for older adults and is considered the gold standard. However, its time-consuming nature can be a limitation in clinical practice. This study found a positive and significant correlation between BOOMER and BBS. This suggests that BOOMER may be a practical and functional alternative to BBS that can be administered in a shorter time.<sup>[14]</sup> Thus, BOOMER may offer clinicians a faster and more accessible assessment option, providing ease of use, especially in busy clinical settings.

In addition to its significant correlation with the BBS, the BOOMER provides several practical advantages in clinical practice. The scale can be administered in a considerably shorter time, requires minimal equipment, and is easy to apply in crowded outpatient settings, home-based rehabilitation, or community health centers where time and resources are limited. Unlike the BBS, which involves 14 separate items and often requires additional space and supervision, the BOOMER combines four brief subtests that

collectively assess static, dynamic, and functional balance.<sup>[15]</sup> This structure not only reduces the physical and cognitive burden on older adults but also enables clinicians to obtain clinically meaningful balance information within minutes. The practicality, time efficiency, and multidimensional nature of the BOOMER make it a highly feasible alternative for routine screenings, rapid fall-risk evaluations, and follow-up assessments in geriatric rehabilitation.<sup>[15,16]</sup>

Moreover, the brevity of the BOOMER allows clinicians to integrate balance assessment into routine evaluations without significantly extending appointment duration.<sup>[16]</sup> This practical feature may increase the likelihood of regular balance monitoring, which is essential for early detection of fall risk. In resource-limited settings where comprehensive assessment tools cannot be used due to time, staff, or space constraints, the BOOMER offers a feasible alternative that maintains clinical relevance without compromising assessment quality.<sup>[14,17]</sup>

The findings reveal that BOOMER is applicable in assessing the balance abilities and fall risk of elderly individuals. The scale has significant clinical potential due to its simplicity, quick application, and coverage of different balance components (static, dynamic, and functional). On the other hand, BBS provides a detailed but more time-consuming reference framework.<sup>[17]</sup> It can also be used in preventive rehabilitation strategies by contributing to the early identification of individuals at high risk of falling.

A major limitation of this study was the relatively small sample size ( $n=60$ ), which may have restricted the generalizability of the findings and reduced the statistical power of certain analyses. The limited number of participants also makes it difficult to fully evaluate the stability of the BOOMER scale across different subgroups of older adults. Furthermore, because test–retest reliability was not assessed, the temporal stability of the BOOMER remains unclear. Future studies should include larger and more diverse samples and incorporate test–retest procedures to evaluate intraclass correlation coefficients, standard error of measurement, and minimum detectable change values.<sup>[18,19]</sup>

Future studies should re-evaluate the validity and reliability of BOOMER using larger samples, different clinical populations, and longitudinal follow-up designs. In particular, it is recommended to calculate the intraclass correlation coefficient, standard error of measurement, and minimum detectable change values to support test–retest reliability.

In addition to these recommendations, future research should also explore the responsiveness of the BOOMER, particularly its ability to detect clinical change following rehabilitation interventions. Establishing responsiveness and minimal clinically important difference (MCID) values would enhance the scale's usefulness in monitoring treatment progress. Furthermore, cross-cultural comparisons between different BOOMER adaptations may provide insight into the scale's broader applicability and help determine whether cultural or population-specific factors influ-

ence balance performance. Examining the performance of BOOMER in clinical subgroups—such as individuals with vestibular disorders, frailty, Parkinson’s disease, or mild cognitive impairment—may also deepen the understanding of its clinical utility and expand its use beyond community-dwelling older adults.

## CONCLUSION

In general, the BOOMER scale is a time-efficient, easy-to-administer, and functional tool for assessing balance in older adults. Its ability to be administered in a shorter time compared to the BBS provides significant practical benefits in the clinical setting. However, further research in different populations is needed to more robustly support its reliability and internal consistency.

### Ethics Committee Approval

Ethical approval was obtained from the Human Research Ethics Board of Marmara University (Date: 30.03.2023, Decision No: 48).

### Informed Consent

All participants provided written informed consent.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: E.A.K., E.T.C ; Design: E.A.K. ; Supervision: E.A.K.; Materials: E.A.K.; Data collection &/or processing: M.M., F.J., M.E.; Analysis and/or interpretation: E.A.K.; Literature search: E.A.K.; Writing: E.A.K.; Critical review: E.A.K.

### Conflict of Interest

None declared.

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## Geriatrik Rehabilitasyonda Denge Sonlanım Ölçeğinin Türkçe Geçerlik ve Güvenirliğı

**Amaç:** Bu çalışma, Geriatrik Rehabilitasyonda Denge Sonlanım Ölçeğinin (GRDSÖ) Türkçe versiyonunun geçerliliğini ve güvenilirliğini belirlemeyi ve psikometrik özelliklerini değerlendirmeyi amaçlamıştır.



**Gereç ve Yöntem:** Çalışmaya 60 yaşlı birey (30 kadın, 30 erkek; yaş ortalaması  $72.03 \pm 7.86$  yıl) dâhil edildi. Katılımcılara GRDSÖ'nün dört alt testi (Adım Testi, Zamanlı Kalk ve Yürü Testi, Fonksiyonel Uzanma Testi, Zamanlı Statik Duruş Testi) ve Berg Denge Ölçeği (BDÖ) uygulandı. Tanımlayıcı istatistikler hesaplanmış, iç tutarlılık için Cronbach alfa ve Kendall'ın W katsayısı kullanılmış, ayrıca Spearman korelasyonu ile madde-toplam ilişkileri ve GRDSÖ ile BDÖ arasındaki korelasyonlar incelendi.

**Bulgular:** GRDSÖ toplam puanı  $12.52 \pm 0.95$  bulunmuştur. Alt testler ile toplam GRDSÖ puanı arasında anlamlı korelasyonlar gözlenmiştir ( $r=0.414-0.565$ ,  $p<0.01$ ). Cronbach alfa katsayısı 0.022 ile düşük bulunmuş, ancak Kendall W katsayısı 0.339 ile orta düzeyde güvenilirlik göstermiştir. BDÖ için başlangıçta alfa 0.304 iken, madde-toplam korelasyon analizi sonrası 0.548'e yükselmiştir. GRDSÖ toplam puanı ile BDÖ toplam puanı arasında pozitif ve anlamlı korelasyon saptanmıştır ( $r=0.419$ ,  $p=0.001$ ).

**Sonuç:** GRDSÖ ölçeği, yaşlı bireylerde statik, dinamik ve fonksiyonel dengeyi kısa sürede değerlendirebilen pratik bir ölçektir. BDÖ ile gösterdiği anlamlı korelasyon, ölçeğin eşzamanlı geçerliliğini desteklemektedir. Bununla birlikte, düşük iç tutarlılık değerleri göz önünde bulundurulurken, farklı popülasyonlarda ve daha büyük örneklerle yapılacak ileri çalışmalarla güvenilirlik bulgularının güçlendirilmesi önerilmektedir.

**Anahtar Sözcükler:** Berg Denge Ölçeği; denge; geçerlilik; güvenilirlik; yaşlı.

# Incidence and Trends of Hepatitis B, Hepatitis C, and HIV among Pregnant Women: A Retrospective Cross-Sectional Study

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**Keywords:** AIDS; HBV; HCV; HIV; incidence; pregnancy



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## ABSTRACT

**Objective:** This retrospective cross-sectional study aimed to investigate the incidence and trends of hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and rates of Hepatitis B surface antibody (anti-HBs) positivity among pregnant women attending an outpatient obstetrics clinic.

**Methods:** Over a four-year period, data from 11,641 antenatal records were analyzed to determine the incidence and trends of anti-HBs, HBV, HCV, and HIV among pregnant women. Screening for anti-HBs, HBsAg, anti-HCV, and anti-HIV antibodies were categorized as positive or negative. People with multiple pregnancies were only counted once for their first positive. Descriptive statistics, chi-square tests for trend analysis, and Poisson distribution were utilized for data analysis.

**Results:** The study revealed varying incidence rates of HBsAg, anti-HCV, and anti-HIV between 1.6-9.2%, 0.2-1.2%, and 0-0.6%, respectively. Absence of HIV cases in 2020 and 2021 changed in 2022 with a 0.2% increase, escalating to 0.6% in 2023. The analysis of anti-HBs levels and HBsAg positivity supported the importance of maternal immunity and HBV infection.

**Conclusion:** Routine screening for HBV, HCV, and HIV is crucial during pregnancy to prevent vertical transmission and improve maternal and infant health outcomes. Understanding the importance of maternal immunity and implementing targeted interventions and public health strategies to reduce transmission rates among pregnant women is essential for achieving this goal.

## INTRODUCTION

Chronic infections of hepatitis B virus (HBV) and hepatitis C virus (HCV) affect approximately 296 million (3.8%) and 58 million (0.8%) individuals, respectively, and making them leading causes of cirrhosis and liver cancer on a global scale.<sup>[1]</sup> Concurrently, the estimated number of people living with human immunodeficiency virus (HIV) reached 39.0 million by the end of 2022, with a rise attributed to improved treatment outcomes and continued new HIV infections.<sup>[2]</sup> In 2019, over 3 million new cases of HBV and HCV infections were reported globally, resulting in a mortality rate exceeding 1.1 million due to these pathogens.<sup>[3]</sup> Likewise, despite the availability of antiretroviral therapy (ART), the year 2022 witnessed a total of 630,000 deaths associated with acquired immunodeficiency syndrome (AIDS) caused by HIV.<sup>[2]</sup> Besides, each of

these three viruses is transmissible via sexual intercourse, parenteral pathways like blood transfusions or needle sharing, and vertical transmission from an infected mother to her baby during gestation or delivery.

The prevalence of hepatitis B, hepatitis C, and HIV varies among pregnant women globally, ranging from 1% to 5% for hepatitis B and C and up to 30% for HIV in regions such as sub-Saharan Africa.<sup>[4,5]</sup> The impact of HBV infection on the risk of obstetric complications is still unclear. However, research findings suggest that HBV infection may pose a risk of preterm birth, gestational diabetes, and antepartum hemorrhage.<sup>[6,7]</sup> On the other hand, it is evident that pregnancies affected by HCV are susceptible to premature rupture of membranes, preterm birth, low birth weight, and gestational diabetes in cases of excessive maternal weight gain.<sup>[8,9]</sup> In addition to the risks of adverse events associated with HIV/AIDS during pregnancy, po-

tential side effects of ART, including psychiatric disorders, liver and kidney issues, gestational diabetes, anemia, small-for-gestational-age infants, and premature deliveries, must also be considered.<sup>[10]</sup>

Of the trio of viral infections discussed, only HCV is curable, however, it is crucial to promptly identify pregnant women with viral infections to initiate interventions that can prevent mother-to-child transmission.<sup>[11]</sup> This study aims to estimate the incidences of HBV, HCV, and HIV among pregnant women and assess the rates of Hepatitis B surface antibody (anti-HBs) positivity as a secondary objective, contributing to the understanding of viral infections during pregnancy.

## MATERIALS AND METHODS

This study was designed as a population-centric, retrospective, and cross-sectional analysis. The study was conducted at an outpatient obstetrics clinic within a tertiary health care facility, with information gathered from antenatal records dating from January 2020 to January 2024. The results of the screenings for anti-HBs, HBsAg, anti-HCV, and anti-HIV antibodies were determined as either positive or negative and documented accordingly. A positive result was determined when the concentration of anti-HBs antibodies reached or exceeded 10 mIU/mL.<sup>[12]</sup> Owing to our access to personal data within the system, individuals experiencing multiple pregnancies over the years were counted only once for their initial application positivity, without duplicating their subsequent pregnancy outcomes. There were no further criteria for exclusion. Maternal sociodemographic information such as maternal age, parity, education level, marital status, and tobacco or alcohol consumption during pregnancy was determined from the same antenatal records.

This study was approved by the Local Ethics Committee on May 13, 2020, under Decision No. 2020/154/177/38 and conducted according to the Declaration of Helsinki. Informed consent was not applicable as this was a retrospective analysis of existing data.

In order to ascertain the incidences of hepatitis B and hepatitis C among pregnant women, the number of hepatitis B or hepatitis C cases was divided by the total number of pregnancies for that year and subsequently multiplied by 100. An identical approach was implemented in the incidence of HIV/AIDS.

**Table 1.** Characteristics of pregnant women

	n (%)
Maternal age	28.72±5.98 (15-50)*
Parity	1.20±1.08 (0-6)*
Educational level, n (%)	
Primary school	4287 (36.8%)
Lower secondary school	5079 (43.6%)
Upper secondary school	2117 (18.2%)
Higher education	158 (1.4%)
Marital status, n (%)	
Married	10128 (87%)
Single	1513 (13%)

\*Values as mean± standard deviation(minimum-maximum).

All statistical analyses were conducted using IBM® SPSS® software version 24 (IBM SPSS Armonk, NY). Descriptive statistics were used to summarize continuous variables, presented as mean with standard deviation, minimum, and maximum values, and categorical variables, reported as counts with percentages. Chi-square for trend tests were used to examine trends in HBV, HCV, and HIV across the study period. Given the rarity of infection among the pregnant women in our study cohort, we adopted a Poisson distribution for our data analysis.

## RESULTS

A total of 11641 pregnant women were included in for the study. 3.8% of the pregnant women were smokers (n=442) and 0.5% of expectant mothers(n=58) were regularly consuming alcohol during their gestational phase. The characteristics of the women are summarized in Table 1.

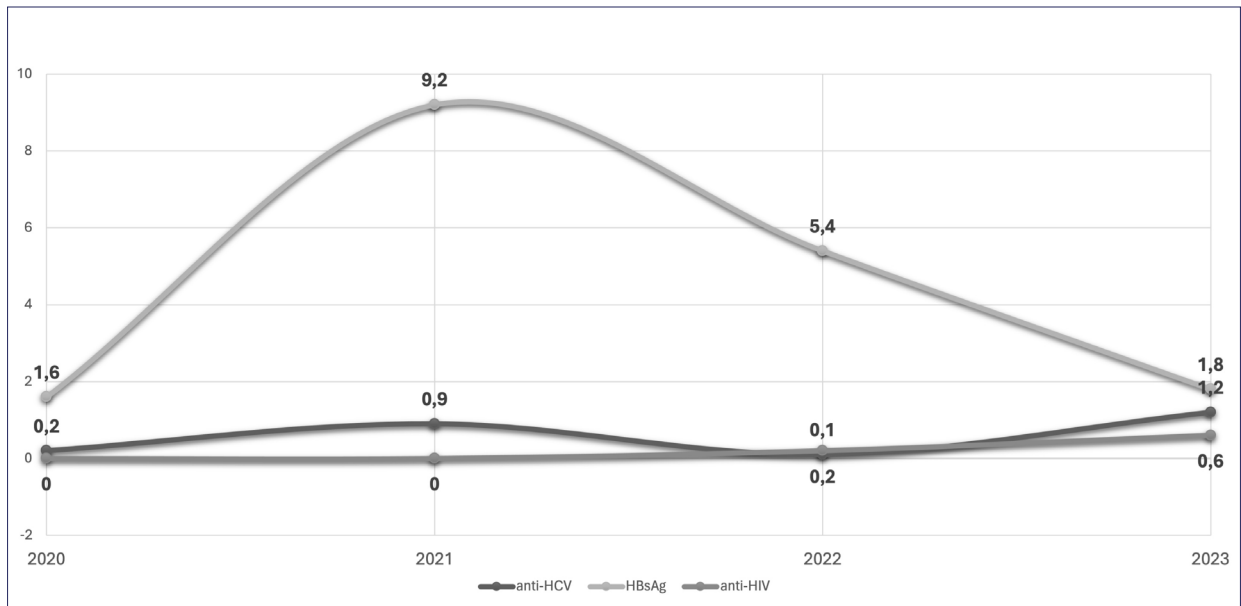
The mean age of the pregnant women on the blood sample day was 28.72±5.98. The mean parity was 1.20±1.08, and 2037 (17.5%) women were nulliparous.

The graph in Figure 1 illustrates the distribution of anti-HCV, HBsAg, and anti-HIV positivity across different years. The information depicted in Figure 2 includes data on both anti-HBs levels and the annual birth counts. Table 2 has further revealed the counts and ratios of HBsAg and anti-HBs values across the years. Two patients in 2023 were found to be positive for anti-HCV, HBsAg, and anti-

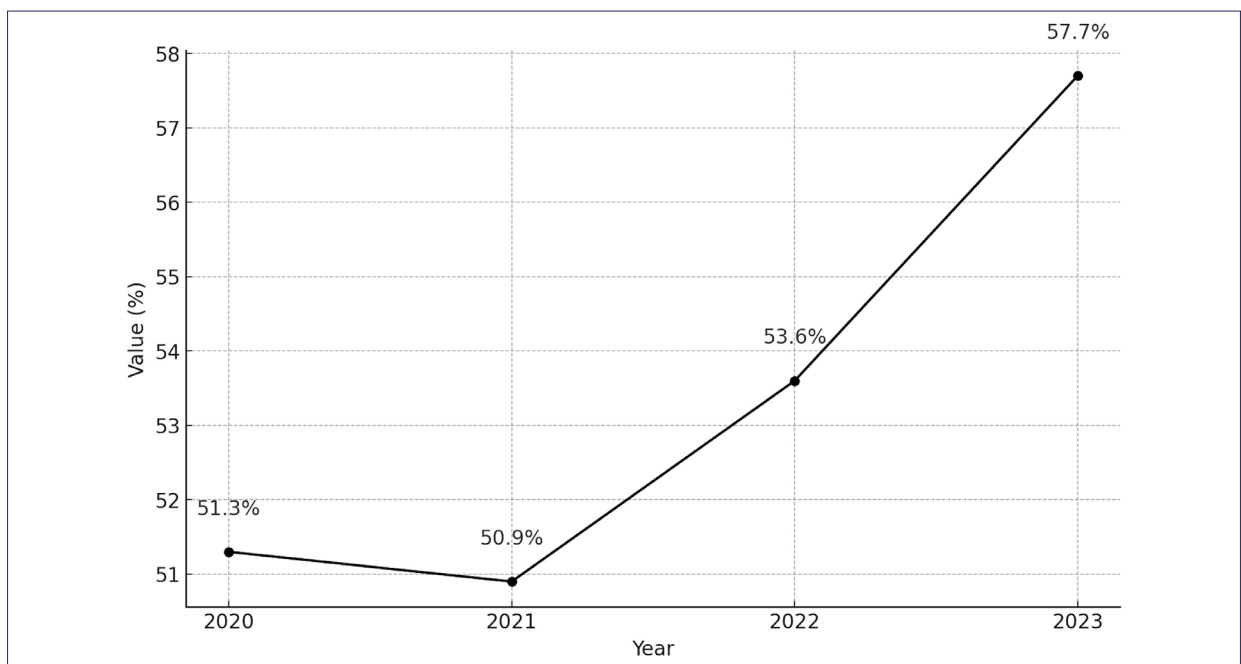
**Table 2.** HBsAg and anti-HBs values across the years

HBsAg	Anti-HBs	2020	2021	2022	2023
+	+	0	0	0	2 (0.05%)
+	-	24 (1.6%)	365 (9.2%)	223 (5.4%)	70 (1.7%)
-	-	719 (47.1%)	1582 (39.9%)	1694 (41%)	1632 (40.6%)
-	+	782 (51.3%)	2017 (50.9%)	2213 (53.6%)	2320 (57.7%)

Values as counts and percentages.



**Figure 1.** The incidences of HBV, HCV, and HIV among pregnant women throughout the years.



**Figure 2.** Annual anti-HBs positivity rates.

HIV. With the exception of these patients, every patient exhibited positivity that was exclusive to a single group.

## DISCUSSION

In our study, we analyzed the levels of HBsAg, anti-HCV, anti-HIV, and anti-HBs in 11641 pregnant patients over a four-year period. During this time, the incidence of HBsAg, anti-HCV, and anti-HIV varied between 1.6-9.2%, 0.2-1.2%, and 0-0.6%, respectively. Anti-Hbs levels showed

fluctuations within the range of 50.9% to 57.7%. The plots of the anti-HBs and HBsAg manifested as symmetrical reflections of one another. In 2020 and 2021, no cases of HIV were reported. However, in 2022, the incidence increased to 0.2%, and by 2023, it had risen to 0.6%.

One possible explanation to interpret the absence of HIV cases, it is essential to recognize the COVID-19 pandemic that was prevalent throughout the entirety of 2020.<sup>[13]</sup> During this period, it was strongly advised by the author-

ities that individuals refrain from visiting hospitals unless it is necessary or in the event of a medical emergency. Due to the three-tiered healthcare framework in our nation, pregnant women predominantly received healthcare at primary health centers during the specified period. On the other hand, while the overall incidence of HIV/AIDS among pregnant women remains relatively low, the increase in cases in 2022 and 2023 appears to be in line with the rise of incidence observed all over the world.<sup>[14]</sup> The absence of reported HIV cases during a particular timeframe may reflect challenges in healthcare access, reporting practices, and stigma associated with the disease. Therefore, continued efforts are needed to ensure accurate tracking and support for individuals affected by HIV/AIDS.

Another aspect to consider in the evaluation is, in comparison to global estimates, the incidence rates of HBV and HCV infections among pregnant women in our study fall within the reported range, with HBV ranging from 1.6% to 9.2% and HCV ranging from 0.2% to 1.2%.<sup>[15]</sup> However, our study rates are higher when compared to research studies exclusively conducted in Turkey.<sup>[16,17]</sup> These rates are consistent with previous studies highlighting the endemic nature of these viral infections and underscoring the importance of antenatal screening and interventions to prevent vertical transmission.<sup>[18]</sup>

Moreover, our findings about the symmetrical reflections noted in the plots of anti-HBs and HBsAg levels among pregnant women support the relationship between maternal immunity and viral replication and indicating the importance of antibodies in protecting against HBV infection.<sup>[19]</sup> While we may be unable to definitively identify whether anti-Hbs positivity arises from vaccination or a past infection, it nevertheless emphasizes the critical importance of the vaccine.<sup>[20,21]</sup>

Despite the valuable insights gained from our study on the incidence of HBV, HCV, and HIV/AIDS among pregnant women, several limitations should be acknowledged. First, the retrospective nature of our study may have introduced bias or limitations in data collection. There may have been inconsistencies or missing data in the antenatal records, potentially affecting the accuracy and completeness of our findings. Additionally, the reliance on electronic health records for data extraction may have limited our ability to capture all relevant variables or information that could have provided further context for the observed trends in viral infection prevalence.

Second, our analysis focused on the incidence of HBV, HCV, and HIV/AIDS among pregnant women without exploring other potential factors that could influence viral transmission or pregnancy outcomes. Factors such as viral load, mode of transmission, maternal immune status, and treatment history were not included in our analysis, limiting the depth of our findings and the ability to draw more nuanced conclusions about the impact of these infections on maternal and infant health.

Despite these limitations, our study offers valuable insights into the incidence of viral infections among pregnant women and highlights the importance of ongoing surveillance, screening, and intervention efforts to improve maternal and infant health outcomes. Future research addressing these limitations could further enhance our understanding of the epidemiology and impact of HBV, HCV, and HIV/AIDS in pregnancy.

## CONCLUSION

In conclusion, the results of this study provide valuable insights into the incidence of hepatitis B, hepatitis C, and HIV/AIDS among pregnant women, highlighting the importance of antenatal screening, vaccination, and education for high-risk populations. Further research can explore the impact of sociodemographic factors on the prevalence of these viral infections among pregnant women, as well as the effectiveness of targeted interventions to reduce transmission rates.

### Ethics Committee Approval

The study was approved by the Local Ethics Committee of Kartal DR. Lütfi Kırdar Training and Research Hospital (Date: 13.05.2020, Decision No: 2020/154/177/38).

### Informed Consent

Retrospective study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: K.T., B.K.; Design: K.T., B.K.; Supervision: K.T., B.K.; Data: B.K.; Analysis: B.K.; Literature search: B.K.; Writing: B.K.; Critical revision: K.T.

### Conflict of Interest

None declared.

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## Gebelerde Hepatit B, Hepatit C ve HIV'in Görülme Sıklığı ve Eğilimleri: Retrospektif Kesitsel Bir Çalışma

**Amaç:** Bu retrospektif kesitsel çalışma, bir poliklinikte periyodik olarak yapılan taramalara katılan gebeler arasında hepatit B virüsü (HBV), hepatit C virüsü (HCV), insan immün yetmezlik virüsü (HIV) ve Hepatit B yüzey antikoru (anti-HBs) pozitiflik oranlarını araştırmayı amaçlamıştır.

**Gereç ve Yöntem:** Dört yıllık bir dönemde, 11,641 gebelik kaydı verileri analiz edilerek anti-HBs, HBV, HCV ve HIV insidans ve trendleri belirlenmiştir. Anti-HBs, HBsAg, anti-HCV ve anti-HIV antikorları için taramalar pozitif veya negatif olarak kategorize edilmiştir. Birden fazla gebeliği olan kişilerde sadece ilk başvurularındaki gebelikteki pozitiflikler sayılmıştır. Veri analizi için tanımlayıcı istatistikler, Poisson dağılımı ve trend analizi için ki-kare testleri kullanılmıştır.

**Bulgular:** Çalışma, HBsAg, anti-HCV ve anti-HIV insidans oranlarının sırasıyla %1.6-9.2, %0.2-1.2 ve %0-0.6 arasında değiştiğini ortaya koymuştur. 2020 ve 2021 yıllarında HIV vakası yokken, 2022 yılında %0.2'lik bir artışla göstermiş ve 2023'te %0.6'ya yükselmiştir. Anti-HBs düzeyleri ve HBsAg pozitifliği analizi, HBV enfeksiyonunda maternal bağışıklığın önemini göstermektedir.

**Sonuç:** Hamilelik sırasında HBV, HCV ve HIV için rutin tarama yapılması, anneden bebeğe bulaşmayı önlemek, anne ve bebek sağlık sonuçlarını iyileştirmek için hayati öneme sahiptir. Maternal bağışıklığın önemini anlamak ve gebelerdeki bulaşma oranlarını azaltmak için hedefe yönelik müdahaleler ve kamu sağlığı stratejileri uygulamak bu amaca ulaşmak için esastır.

**Anahtar Sözcükler:** AIDS; gebelik; HBV; HCV; HIV; insidans.

# How Accurate is Self-Reported Parental Height? Evidence From a Tertiary Pediatric Endocrinology

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**Keywords:** Parental height;  
pediatric endocrinology;  
self-reported height; target  
height.



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## ABSTRACT

**Objective:** Parental height is a key component of growth assessment in children; however, it is often self-reported. The accuracy of reported parental height and its potential clinical implications remain insufficiently studied.

**Methods:** Parents of the first 100 children attending a tertiary pediatric endocrinology clinic for the first time were included. Parental height was first self-reported and subsequently measured using a standardized stadiometer. Height standard deviation scores (SDS) were calculated based on Neyzi reference data. Reporting error was defined as the difference between reported and measured height ( $\Delta$  SDS). Agreement was assessed using Wilcoxon signed-rank tests and Bland–Altman analysis. Correlations were evaluated using Spearman's rank test.

**Results:** A total of 96 mothers and 58 fathers were included. Self-reported height was significantly higher than measured height in both mothers (159.3 $\pm$ 6.1 vs. 157.3 $\pm$ 5.6 cm,  $p$ <0.001) and fathers (174.8 $\pm$ 5.3 vs. 172.7 $\pm$ 4.6 cm,  $p$ <0.001). Over-reporting of  $\geq$ 2 cm was observed in 51.0% of mothers and 58.6% of fathers. Bland–Altman analysis demonstrated a mean bias of 2.0 cm in mothers and 2.3 cm in fathers, with wide limits of agreement. No significant correlation was found between measured height SDS and reporting error in either group. Reporting accuracy was not influenced by parental stature, sex, or shared family behavior.

**Conclusion:** Self-reported parental height frequently overestimates true height and shows substantial individual variability in a pediatric endocrinology setting. Whenever possible, direct measurement of parental height should be incorporated into routine clinical practice to ensure accurate growth assessment.

## INTRODUCTION

Parental height is a fundamental component of growth assessment in children and is routinely used for the calculation of target height and interpretation of growth patterns in pediatric practice.<sup>[1,2]</sup> A child's height centile is evaluated in relation to the mid-parental height (MPH) centile and target range (MPH $\pm$ 2 SD) on the growth chart; height outside this range increases the likelihood of an underlying growth disorder.<sup>[1,3]</sup> Accurate determination of parental height is essential for the assessment of a child's growth potential across a wide range of conditions affecting linear growth, not limited to the evaluation of short stature.<sup>[2,4]</sup>

In pediatric endocrinology clinics, parental height is ideally measured using standardized stadiometry. However, in real-life clinical settings, direct measurement may not always be feasible because of high patient volume or incomplete

parental attendance at the time of evaluation. Consequently, parental height is frequently obtained by self-report, particularly in routine pediatric practice.<sup>[3]</sup> Although self-reported anthropometric data are convenient, they are susceptible to systematic reporting bias and may not reliably reflect true height.<sup>[5,6]</sup>

Previous studies in adult populations have demonstrated that self-reported height tends to be overestimated, with greater discrepancies observed among men and shorter individuals.<sup>[6-8]</sup> However, evidence on the accuracy of self-reported parental height in pediatric clinical settings is scarce, and data from the Turkish population are limited. Moreover, the potential impact of inaccurate parental height reporting on growth assessment and target height calculation has not been sufficiently addressed.<sup>[9]</sup>

The aim of this study was to evaluate the agreement be-

tween reported and measured parental height in a pediatric endocrinology clinic setting. We also aimed to examine differences in reporting accuracy between mothers and fathers, and to determine whether the magnitude of self-reported error can be considered clinically acceptable in the Turkish population.

## MATERIALS AND METHODS

This observational study was conducted at a tertiary pediatric endocrinology outpatient clinic. Parents (96 mother, 58 father) of the first 100 consecutive children who attended the clinic for the first time after scheduling their appointment through the national central appointment system were invited to participate. Both mothers and fathers were eligible for inclusion if they attended the clinic visit. Parents with known skeletal deformities, previous spinal surgery, or medical conditions affecting standing height were excluded from the study.

At the initial clinic visit, parental height was first obtained by self-report and recorded by the clinician. Subsequently, standing height was measured using a calibrated Holtain Harpenden stadiometer by experienced pediatric endocrinologist. Measurements were performed with parents barefoot and positioned in the Frankfurt plane, and height was recorded to the nearest 0.1 cm.

Adult height standard deviation scores (SDS) were calculated separately for reported and measured parental heights using sex-specific mean and standard deviation values at 18 years of age derived from the Neyzi growth charts, which were used as a proxy for adult height.<sup>[10]</sup> The difference between reported and measured SDS values ( $\Delta$  SDS) was used to assess reporting bias.

Written informed consent was obtained from all participating parents prior to enrollment. Participation was voluntary, and all data were anonymized before analysis to ensure confidentiality. Studies were performed with

the approval of the Ethics Committee of the Marmara University Faculty of Medicine, Istanbul, Türkiye (09.2025-25.0954) and according to the Declaration of Helsinki.

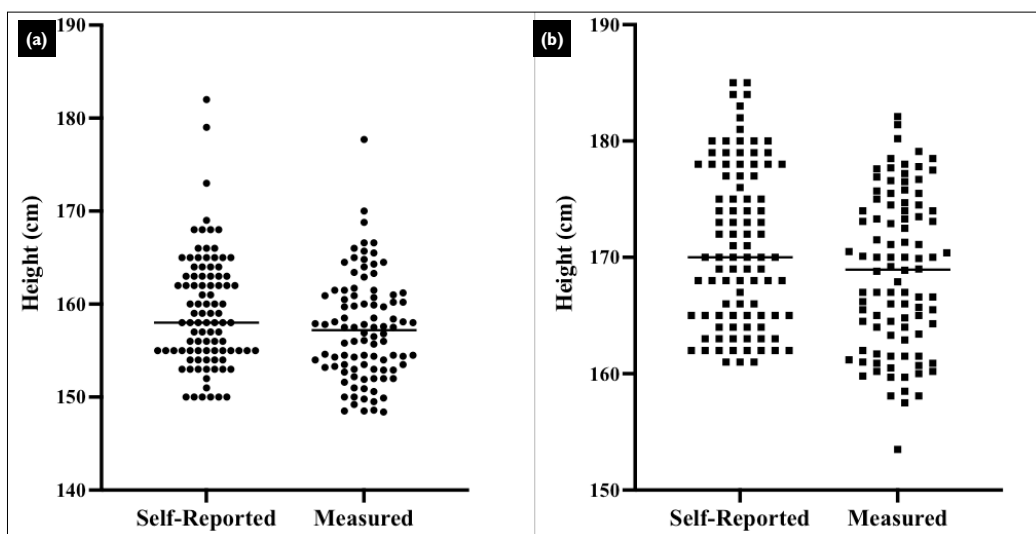
## Statistical analysis

Statistical analyses were performed using GraphPad Prism® version 10 (GraphPad Software Inc., San Diego, California, USA). Statistical significance was defined as  $p < 0.05$ . Continuous variables were summarized as mean  $\pm$  standard deviation or median, as appropriate. Differences between self-reported and measured parental heights were assessed using the Wilcoxon signed-rank test. Agreement between reported and measured height was evaluated using Bland–Altman analysis, including calculation of mean bias and 95% limits of agreement. Associations between measured height SDS and reporting error ( $\Delta$  SDS), as well as between maternal and paternal reporting error, were assessed using Spearman's rank correlation coefficient. Comparisons of reporting error between parents below and above the 25th height percentile were performed using the Mann–Whitney U test.

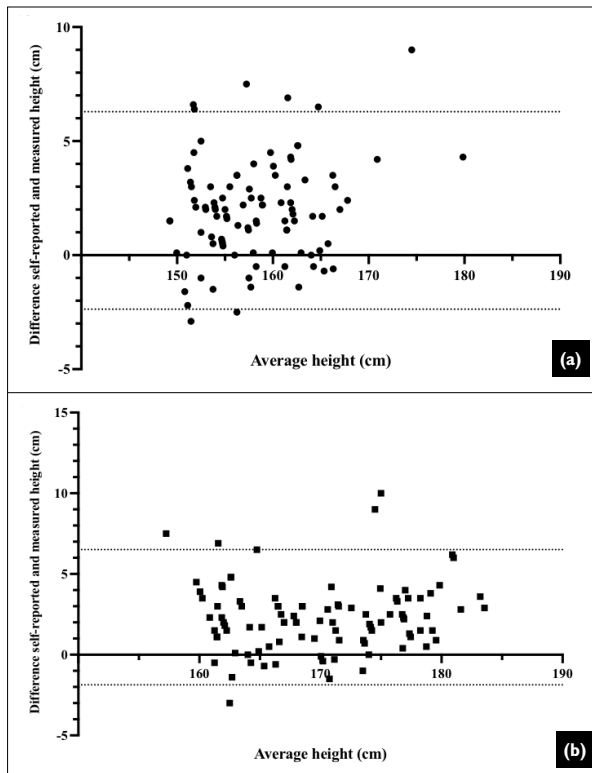
## RESULTS

Of the 100 children included, 54 attended the first clinic visit with both parents, 42 attended with their mother only, and 4 attended with their father only.

Among mothers, self-reported height (median:  $159.3 \pm 6.1$ , range: 150–182 cm) was significantly higher than measured height ( $157.3 \pm 5.6$ , range: 148.4–177.7 cm) ( $p < 0.001$ , Wilcoxon signed-rank test). Similarly, among fathers, self-reported height (median:  $174.8 \pm 5.3$ , range: 161–185 cm) was also significantly higher than measured height (median:  $172.7 \pm 4.6$ , range: 162–182.1 cm) ( $p < 0.001$ , Wilcoxon signed-rank test). Comparison of self-reported and measured parental height demonstrated consistent differences across the distribution in both mothers and fathers (Fig. 1).



**Figure 1.** Comparison of self-reported and measured parental height in (A) mothers and (B) fathers.



**Figure 2.** Agreement Between self-reported and measured parental height assessed by Bland–Altman analysis. Bland–Altman plots showing the agreement between self-reported and measured parental height in (a) mothers and (b) fathers. The difference between self-reported and measured height is plotted against the mean of the two measurements. The solid horizontal line represents the mean difference (bias), and the dashed lines indicate the 95% limits of agreement.

Among mothers, over-reporting of  $\geq 2$  cm was observed in 49 participants (51.0%), while major over-reporting ( $\geq 5$  cm) was present in 7 (7.3%). Under-reporting of  $\leq -2$  cm was observed in 3 mothers (3.1%). Among fathers,

over-reporting of  $\geq 2$  cm was observed in 34 participants (58.6%), while major over-reporting ( $\geq 5$  cm) was present in 3 (5.2%). Under-reporting of  $\leq -2$  cm was observed in 1 father (1.7%).

Bland–Altman analysis demonstrated a positive mean bias in mothers (2.0 cm; 95% limits of agreement:  $-2.4$  to  $+6.3$  cm) and fathers (2.3 cm;  $-1.9$  to  $+6.5$  cm), indicating higher self-reported than measured height. In both groups, wide 95% limits of agreement were observed, reflecting considerable individual variability (Fig. 2).

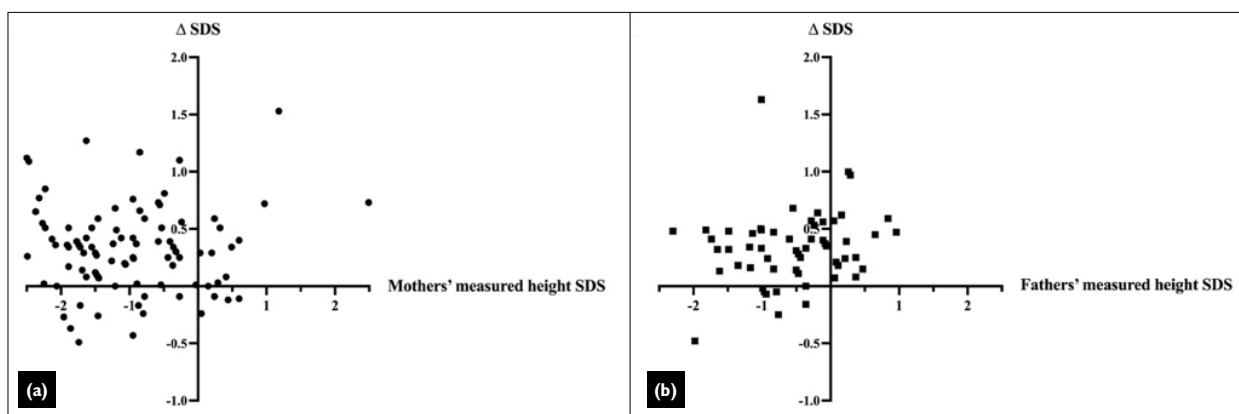
When measured height SDS was compared with reporting error ( $\Delta$  SDS), no significant correlation was observed in either mothers (Spearman's  $\rho = -0.05$ , 95% CI  $-0.20$  to  $0.20$ ,  $p = 0.66$ ;  $n = 96$ ) or fathers ( $\rho = 0.10$ , 95% CI  $-0.10$  to  $0.40$ ,  $p = 0.36$ ;  $n = 58$ ), indicating that reporting accuracy was not influenced by parental height (Fig. 3). When mothers and fathers were stratified according to measured height below and above the 25th percentile, no significant differences in reporting error were observed between the two groups in either parent ( $p = 0.67$  and  $p = 0.31$  respectively).

Among families in which both parents attended the clinic, no significant correlation was observed between maternal and paternal reporting error ( $\Delta$  SDS) (Spearman's  $\rho = 0.20$ , 95% CI  $-0.10$  to  $0.40$ ,  $p = 0.19$ ;  $n = 54$ ).

## DISCUSSION

In this study, we evaluated the agreement between self-reported and measured parental height in a tertiary pediatric endocrinology clinic and demonstrated that both mothers and fathers systematically overestimated their height. Self-reported values were significantly higher than measured values in both groups, with a mean overestimation of approximately 2 cm. These findings are consistent with previous reports in adult populations showing a tendency toward height over-reporting.<sup>[5-7,11]</sup>

Bland–Altman analysis revealed wide limits of agreement,



**Figure 3.** Scatter plots showing the relationship between measured height standard deviation score (SDS) and reporting error ( $\Delta$  SDS) in (a) mothers and (b) fathers.  $\Delta$  SDS was calculated as the difference between self-reported and measured height SDS. No significant correlation was observed between measured height SDS and reporting error in either group, indicating that reporting accuracy was not influenced by parental stature.

indicating substantial individual variability in reporting accuracy.<sup>[12]</sup> Although the average bias was modest, discrepancies of up to 6-7 cm were observed in both mothers and fathers. Such differences may be clinically relevant, as inaccurate parental height reporting can affect mid-parental height calculation and the interpretation of a child's growth pattern.<sup>[3,13]</sup>

More than half of the parents over-reported their height by at least 2 cm, while major discrepancies of 5 cm or more were present in a considerable minority. In contrast, under-reporting was uncommon. These findings suggest that over-reporting represents the predominant pattern of bias in this population, in line with previous anthropometric validation studies.<sup>[5,6]</sup>

Unlike some previous studies reporting greater overestimation among shorter individuals,<sup>[6,14]</sup> we did not observe an association between measured height and reporting error. Neither correlation analyses nor stratification by height percentile revealed differences in reporting accuracy among shorter parents, suggesting that reporting bias occurred independently of actual stature.

Previous studies conducted predominantly in adult populations have reported greater overestimation among men than women.<sup>[4,6,7,14]</sup> In contrast, our findings did not support the hypothesis that men tend to overestimate their height more than women. This discrepancy may reflect cultural and contextual differences in health-related perceptions and reporting behaviors. In the Turkish population, height perception and self-reporting practices may be less influenced by gender-related social and increased health awareness among parents attending pediatric specialty clinics may contribute to similar reporting patterns between mothers and fathers.

Notably, a substantial proportion of children attended the first clinic visit without their fathers, and paternal height was therefore frequently obtained by self-report. This reflects common patterns in routine pediatric practice in Turkey, where mothers more often accompany children to outpatient visits. Sociocultural and occupational factors, including work-related constraints and traditional caregiving roles, may limit paternal attendance. Consequently, clinicians frequently rely on indirectly obtained paternal anthropometric data, which may further increase the risk of reporting bias.

Interestingly, a population-based study from Scotland reported that both men and women tended to underestimate their height, with mean differences of 1.3 cm and 1.7 cm, respectively.<sup>[15]</sup> Despite differences in the direction of reporting bias, a consistent finding across studies is the wide individual variability between reported and measured height in both sexes. This reinforces the importance of accurate parental height measurement in pediatric clinical practice. In addition, no significant correlation was observed between maternal and paternal reporting error among families in which both parents attended the clinic, suggesting that reporting accuracy reflects individual

rather than shared family-related behavior.

From a clinical perspective, these findings highlight the limitations of relying solely on self-reported parental height in pediatric growth assessment. Given the frequency and magnitude of reporting errors, direct measurement of parental height should be encouraged whenever feasible.<sup>[3,13]</sup> When measurement is not possible, clinicians should interpret reported values with caution and consider potential bias. Efforts should be made to measure both parents at the earliest opportunity and to record their heights in the child's health record.

The main strengths of this study include the standardized measurement protocol, the use of Bland–Altman analysis, and the focus on a pediatric endocrinology population. However, several limitations should be acknowledged. The single-center design may limit generalizability, and socioeconomic and educational factors that may influence reporting accuracy were not assessed.

## CONCLUSION

In conclusion, self-reported parental height frequently overestimates true height and shows substantial individual variability in a pediatric endocrinology setting. These discrepancies are not influenced by parental stature, sex or shared family behavior. Whenever possible, direct measurement of parental height should be incorporated into routine clinical practice to ensure accurate growth assessment.

### Ethics Committee Approval

Studies were performed with the approval of the Ethics Committee of the Marmara University Faculty of Medicine (Date: 21.11.2025, Decision No: 09.2025-25.0954).

### Informed Consent

Written informed consent was obtained from all participating parents prior to enrollment.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: B.G.T., T.G.; Design: B.G.T., T.G.; Supervision: Z.Y.A.; Materials: B.G.T.; Data collection &/or processing: B.G.T., M.E., D.H.; Analysis and/or interpretation: B.G.T., D.H.; Literature search: B.G.T., Z.Y.A.; Writing: B.G.T., M.E.; Critical review: Z.Y.A., T.G.

### Conflict of Interest

None declared.

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## Ebeveynlerin Beyan Ettikleri Boy Ölçümlerinin Güvenilirliği: Üçüncü Basamak Bir Çocuk Endokrinoloji Merkezinden Bulgular

**Amaç:** Ebeveyn boyu, çocuklarda büyümenin değerlendirilmesinde temel bir bileşen olmakla birlikte, çoğu zaman beyan ettikleri boy kabul edilir. Ancak ebeveynlerin bildirdiği boy ölçümlerinin doğruluğu ve bunun olası klinik sonuçları yeterince araştırılmamıştır.

**Gereç ve Yöntem:** Üçüncü basamak bir çocuk endokrinoloji kliniğine ilk kez başvuran ilk 100 çocuğun ebeveynleri çalışmaya dâhil edildi. Ebeveynlerin boyları önce öz bildirim yoluyla alındı, ardından standart bir stadiometre kullanılarak ölçüldü, boy standart sapma skorları (SDS) hesaplandı. Bildirim hatası, bildirilen ve ölçülen boy arasındaki fark ( $\Delta$  SDS) olarak tanımlandı. Uyum, Wilcoxon işaretli sıralar testi ve Bland–Altman analizi ile değerlendirildi. Korelasyon analizleri Spearman sıra korelasyon testi ile yapıldı.

**Bulgular:** Çalışmaya toplam 96 anne ve 58 baba alındı. Hem anneler hem de babalar boylarını, ölçülen değerlere göre anlamlı olarak daha uzun bildirdi (anneler:  $159.3 \pm 6.1$  ve  $157.3 \pm 5.6$  cm; babalar:  $174.8 \pm 5.3$  ve  $172.7 \pm 4.6$  cm; her ikisi için  $p < 0.001$ ). Annelerin %51.0'i, babaların ise %58.6'sı boyunu en az 2 cm daha uzun bildirmişti. Bland–Altman analizi, annelerde ortalama 2.0 cm, babalarda ise 2.3 cm'lik fazla bildirim olduğunu ve bireyler arasında belirgin farklılıklar bulunduğunu gösterdi. Ölçülen boy SDS ile  $\Delta$  SDS arasında anlamlı bir ilişki saptanmadı. Ayrıca, bildirim doğruluğu ebeveynin boyu, cinsiyeti veya aile içi ortak davranışlardan etkilenmedi.

**Sonuç:** Çocuk endokrinoloji pratiğinde ebeveynlerin bildirimine dayalı boy ölçümleri, gerçek boyu sıklıkla olduğundan yüksek göstermekte ve belirgin bireysel değişkenlik içermektedir. Büyümenin doğru değerlendirilmesini sağlamak için, mümkün olan durumlarda ebeveyn boylarının doğrudan ölçülmesi rutin klinik uygulamaya dâhil edilmelidir.

**Anahtar Sözcükler:** Bildirime dayalı boy; çocuk endokrinolojisi; ebeveyn boyu; hedef boy.

# The Relationship Between Attention Deficit Hyperactivity Disorder Symptoms and Forgiveness Behavior Pattern in Antisocial Personality Disorder

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**Keywords:** Antisocial personality disorder; attention deficit hyperactivity disorder; forgiveness.



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## ABSTRACT

**Objective:** This study aimed to examine the relationship between Attention Deficit Hyperactivity Disorder (ADHD) symptom severity and forgiveness behavior among individuals with Antisocial Personality Disorder (ASPD), both with and without comorbid ADHD, in comparison to a healthy control group.

**Methods:** The sample consisted of 190 male participants divided into three groups: ASPD with ADHD symptoms (n=52), ASPD without ADHD symptoms (n=38), and a healthy control group (n=100). Diagnoses were established through structured clinical interviews based on DSM-V-TR criteria. Participants completed the Adult ADHD Symptom Scale and the Forgiveness Scale. Correlation analyses were conducted separately for each group to explore the association between ADHD symptom scores and forgiveness.

**Results:** Sociodemographic variables were evenly distributed across all groups. A significant negative correlation was observed between ADHD symptoms and forgiveness in the ASPD without ADHD group ( $r=-0.418$ ,  $p=0.008$ ), indicating that increased ADHD symptoms in this group were associated with lower forgiveness. In contrast, a positive correlation was found in the ASPD with ADHD group ( $r=0.104$ ,  $p=0.043$ ) and the healthy control group ( $r=0.196$ ,  $p=0.005$ ), suggesting that higher ADHD symptoms may be related to increased forgiveness in these populations.

**Conclusion:** The findings suggest that ADHD symptoms may modulate emotional responsiveness and forgiveness behavior, even in individuals with antisocial traits. The presence of forgiving behavior in antisocial individuals may reflect ADHD-related emotional variability rather than the absence of antisocial pathology. These results highlight the diagnostic complexity between ADHD and ASPD and underline the importance of multidimensional assessment in clinical practice.

## INTRODUCTION

Antisocial Personality Disorder (ASPD) is a mental health condition characterized by a persistent disregard for the rights of others, accompanied by irresponsible, aggressive, and rule-breaking behaviors.<sup>[1]</sup> Individuals with ASPD frequently exhibit chronic patterns of illegal behavior; impulsivity, hostility, physical aggression, and poor adherence to social norms.<sup>[2]</sup> In addition to overt behavioral problems, impairments in social relationships, emotional coldness, lack of remorse, and diminished concern for others' feelings are commonly observed.<sup>[3]</sup> These enduring personality features often lead to significant functional impairments across multiple life domains.<sup>[3,4]</sup> ASPD is also frequently associated with comorbid psychiatric conditions, particularly

substance use disorders, and is linked to increased rates of both natural and unnatural mortality.<sup>[5]</sup>

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder defined by persistent symptoms of inattention, hyperactivity, and impulsivity that interfere with daily functioning.<sup>[6]</sup> In adulthood, ADHD symptoms may present as difficulties in sustaining attention, impaired impulse control, emotional instability, and challenges in occupational and social functioning.<sup>[7]</sup> An increasing body of literature demonstrates a strong association between ADHD and ASPD, with ADHD symptoms often preceding or accompanying antisocial behaviors, particularly from adolescence onward.<sup>[8]</sup> Individuals with comorbid ADHD and ASPD tend to exhibit more severe behavioral dysreg-

ulation, greater functional impairment, and poorer long-term outcomes compared to individuals diagnosed with either disorder alone.<sup>[5,9]</sup>

From a neurobiological and psychological perspective, ADHD and ASPD appear to share overlapping mechanisms, particularly in domains related to impulse control, emotional regulation, and executive functioning.<sup>[10]</sup> These shared vulnerabilities may contribute to the high comorbidity observed between the two disorders and complicate diagnostic differentiation.<sup>[11,12]</sup> While ASPD is typically associated with emotional detachment and reduced empathy, ADHD has been linked to emotional reactivity and affective instability, suggesting that individuals with overlapping symptom profiles may demonstrate more heterogeneous interpersonal characteristics than traditionally assumed.<sup>[2]</sup>

Beyond core diagnostic symptoms, interpersonal processes such as forgiveness represent an important yet underexplored dimension in individuals with ASPD and ADHD.<sup>[13]</sup> Forgiveness is generally defined as the willingness to reduce resentment, negative judgment, and retaliatory motivations toward an offender.<sup>[13]</sup> Low levels of forgiveness have been associated with increased aggression, interpersonal conflict, and emotional dysregulation—features frequently observed in both ADHD and ASPD populations.<sup>[14]</sup> Previous studies have also reported associations between ADHD symptom severity and forgiveness-related tendencies, suggesting that attentional and emotional dysregulation may influence interpersonal responses to perceived wrongdoing.<sup>[15-17]</sup>

Despite the established links between ADHD, ASPD, and interpersonal dysfunction, the role of forgiveness within this relationship remains insufficiently investigated. Understanding how forgiveness relates to ADHD symptom severity in individuals with ASPD may provide valuable insights into the emotional and interpersonal mechanisms underlying these complex clinical presentations. Therefore, the present study aims to examine the association between ADHD symptoms and forgiveness behavior in individuals diagnosed with ASPD, both with and without comorbid ADHD, in comparison to a healthy control group. Clarifying these relationships may contribute to more nuanced clinical assessments and inform targeted intervention strategies aimed at improving interpersonal functioning and reducing maladaptive behaviors in this population.

## MATERIALS AND METHODS

The study recruited a sample of 90 male adults diagnosed with ASPD using the Structured Clinical Interview for DSM Disorders (SCID), administered by a psychiatrist from Kartal Dr Lutfi Kirdar City Hospital between January 2023 and June 2023. Participants were randomly selected among individuals diagnosed with ASPD and included in the study on a voluntary basis. The study procedures were conducted according to the Declaration of Helsinki. Additionally, the study was approved by the Kartal Dr. Lutfi

Kirdar City Hospital Clinical Research Ethics Committee under decision number 2018/514/139/1 and 12/10/2018 date. After the participants were informed about the study by a researcher, the written informed consent was obtained. The inclusion criteria were as follows: Having a diagnosis of ASPD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR) diagnostic criteria, being literate, and agreeing to participate in the study. Patients with active psychotic symptoms, being under the influence of a substance, meeting the diagnostic criteria for mood disorder, and having psychiatric or organic mental disorders other than ASPD that may cause impulsivity/behavior disorder were excluded from the study. After all exclusions, a total of 90 individuals with ASPD were evaluated. Besides, healthy control group (n=100) was also evaluated as part of the comparison group. For this group, participants were required to be between the ages of 18 and 65, have no current or past psychiatric diagnosis, no history of psychiatric treatment, no use of psychotropic medication, and no history of substance or alcohol dependence or neurological illness. Additionally, individuals scoring below the clinical threshold on the ADHD symptom scale and without significant attention or impulse control complaints were included. All participants had to be literate and provide informed consent.

Exclusion criteria for the control group included any current or past diagnosis of a psychiatric or neurodevelopmental disorder (including ADHD, depression, anxiety, bipolar disorder, or personality disorders), current use of psychotropic medication, a history of neurological disease or head trauma, and ongoing substance use or dependence. Participants who failed to meet these criteria were excluded to preserve the integrity of the comparison group.

Data were collected through standardized measurement inventories and scales administered to the participants. In particular, DSM-V criteria were taken into consideration in the assessment of ASPD and ADHD symptoms. Participants were assessed using a sociodemographic information form, the Attention Deficit Hyperactivity Disorder Symptom Scale, and the Forgiveness Scale.

### Outcome measures

A structured sociodemographic questionnaire developed by the researcher was applied to determine the sociodemographic characteristics of the individuals.

Structured Clinical Interview for DSM-V I and II (SCID I and SCID II) which was administered by a psychiatrist and developed according to DSM-V diagnostic criteria, was used in the diagnostic interviews of the patients. SCID I is a structured interview for clinical psychiatric diagnoses in accordance with DSM-V criteria and SCID II is a structured interview for diagnosing personality disorders. Turkish validity and reliability studies of the SCID were conducted by Çorapçıoğlu et al.<sup>[18]</sup>

The Adult Attention Deficit Hyperactivity Disorder Symptom Scale is a 30-item self-report measure that assesses the presence and severity of ADHD symptoms across the domains of attention deficit, hyperactivity/impulsivity, and characteristics associated with attention deficit disorder/attention deficit hyperactivity disorder.<sup>[19]</sup>

Forgiveness Scale is a validated self-report measure assessing the level of forgiveness of individuals. The scale consists of 10 questions and the total score ranges from 10 to 50. The Turkish validity and reliability of the scale was conducted by Sariçam et al.<sup>[20]</sup>

All assessments were administered face-to-face by the researcher to the individuals included in the study in the form of a questionnaire.

### Statistical analyses

The data were analyzed using Statistical Package for the

Social Sciences (SPSS) (Version 25.0; SPSS Inc., Chicago, Illinois, USA) statistical software. Number, percentage, mean values, and standard deviations were used. Descriptive statistics, and correlation analyses were used to examine the relationships between ADHD symptoms, forgiveness, and ASPD symptoms. Pearson correlation analysis was conducted separately for each group to examine the relationship between ADHD symptom severity and forgiveness tendency. A p-value less than 0.05 was considered statistically significant.

## RESULTS

A total of 190 participants were included in the study, consisting of individuals with ASPD with ADHD symptoms (n=52), ASPD without ADHD symptoms (n=38), and control group (n=100). The groups were compared in terms of age, education level, marital status, economic status,

**Table 1.** Sociodemographic characteristics between groups

	ASPD without ADHD (n=38)	ASPD with ADHD (n=52)	Control Group (n=100)	F/ $\chi^2$	p
Age (year $\pm$ SD)	35.40 $\pm$ 9.02	38.32 $\pm$ 11.01	36.55 $\pm$ 10.38	2.77	0.065
Education level					
Illiterate	2	3	5	14.10	0.55
Primary school	10	13	25		
Middle school	11	15	30		
High school	9	13	25		
University	6	8	15		
Marital status					
Married	13	18	35	20.04	0.61
Single	19	26	50		
Divorced	6	8	15		
Economic status					
Low	19	26	50	13.62	0.74
Middle	13	18	35		
Good	6	8	15		
Current Employment status					
Employed	21	29	55	37.86	0.82
Unemployed	17	23	45		
History of suicide					
Yes	8	10	20	52.21	0.59
No	30	42	80		
Substance use status					
Never used	10	13	25		
Currently using	19	26	50	30.07	0.67
Used in the past, but quit	9	13	25		
Smoking status					
Never smoked	11	16	30	37.99	0.71
Currently smoking	19	26	50		
Used to smoke, but quit	8	10	20		

Mean and standard deviations were expressed as X $\pm$ SD, SD: Standard deviation, p<0.05,  $\chi^2$ : Ki-kare; ASPD: Antisocial Personality Disorder, ADHD: Attention Deficit Hyperactivity Disorder.

**Table 2.** Correlation between attention deficit hyperactivity disorder symptoms and forgiveness for groups

Variable	Attention Deficit Hyperactivity Disorder Symptom Scale-Total Score					
	ASPD without ADHD (n=38)		ASPD with ADHD (n=52)		Control Group (n=100)	
	r	p	r	p	r	p
Forgiveness Scale	-0.418***	0.008*	0.104**	0.043*	0.196**	0.005*

\*\*\*The correlation is significant at the 0.05 level, \*\* The correlation is significant at the 0.01 level, \*p<0.05.

employment, history of suicide, substance use, and smoking status.

There were no statistically significant differences between the groups in terms of age, education level, marital status, economic status, employment status, history of suicide, substance use, and smoking status ( $p>0.05$ ). Additionally, the groups demonstrated a homogeneous distribution in terms of sociodemographic variables (Table 1).

As shown in Table 2, a statistically significant negative correlation was found between ADHD symptom scores and forgiveness in the ASPD without ADHD group ( $r=-0.418$ ,  $p=0.008$ ). This indicates that as ADHD symptom severity increases within this group, forgiveness tendencies decrease (Table 2).

In the ASPD with ADHD group, a statistically significant positive correlation was observed between ADHD symptom scores and forgiveness ( $r=0.104$ ,  $p=0.043$ ). This suggests that higher ADHD symptom severity may be related to increased forgiveness tendencies in individuals with comorbid ASPD and ADHD (Table 2).

Furthermore, the control group also demonstrated a statistically significant positive correlation between ADHD symptom scores and forgiveness ( $r=0.196$ ,  $p=0.005$ ), though the strength of the association was modest. This may indicate that mild attentional or emotional variability within non-clinical populations could be related to more flexible or emotionally responsive interpersonal behaviors (Table 2).

## DISCUSSION

The present study explored the relationship between ADHD symptom severity and forgiveness behavior in individuals with ASPD, both with and without comorbid ADHD, in comparison to a healthy control group. Our findings indicated that healthy individuals, who had no psychiatric diagnoses including ADHD, demonstrated the highest levels of forgiveness. Importantly, among individuals with both ASPD and ADHD symptoms, a positive correlation was observed between ADHD symptom severity and forgiveness. In contrast, individuals with ASPD without ADHD exhibited significantly lower forgiveness scores and showed a negative correlation between ADHD symptoms and forgiveness. These results suggest that the presence of ADHD symptoms may be associated with more emotionally responsive and forgiving behavior even in the

context of antisocial traits, and that individuals showing forgiving tendencies may be more likely to have ADHD rather than pure antisocial pathology.

These findings are consistent with Shaw et al.<sup>[21]</sup> who reported that ADHD is often accompanied by emotional dysregulation, heightened sensitivity, and fluctuating empathy, which can manifest in socially adaptive behaviors such as forgiveness.<sup>[21]</sup> Similarly, Barkley noted that impulsivity in ADHD does not always result in destructive behavior but can also lead to emotionally motivated responses such as guilt, remorse, and reconciliation.<sup>[22]</sup> These characteristics could explain the more prosocial tendencies observed in ASPD individuals with ADHD symptoms. On the other hand, some studies have emphasized the emotional rigidity and impaired empathy in ADHD, which contrasts with our results. For example, Graziano et al.<sup>[23]</sup> argued that persistent emotional dysregulation in ADHD is associated with difficulties in empathy and forgiveness, especially in emotionally charged interpersonal contexts. The current study findings support the notion that emotional impulsivity or variability characteristic of ADHD may facilitate affective responses such as forgiveness, even in the context of antisocial traits. Moreover, this perspective suggests a more consistently impaired social-emotional profile in ADHD than what was observed in our study.

In individuals with ASPD but without ADHD, our study revealed a lack of forgiveness and a negative association with ADHD symptom scores. This aligns with existing literature emphasizing the callous-unemotional traits, low remorse, and poor interpersonal functioning typically found in individuals with ASPD. Frick et al.<sup>[24]</sup> described these emotional deficits as stable and relatively unresponsive to environmental or contextual factors, reinforcing our findings that forgiveness is less likely in "pure" antisocial presentations. While our findings are in line with those emphasizing the affective coldness in ASPD, some researchers have argued for variability even within ASPD presentations. For instance, some subtypes of ASPD have been reported to show situational emotional responses depending on social context or comorbid features. However, such perspectives remain less prominent and were not supported by the forgiveness patterns in our study. Furthermore, although these individuals do not meet criteria for ADHD, subclinical symptom elevations may be associated with more rigid or less prosocial interpersonal functioning.

Healthy control participants in our study showed the highest forgiveness scores overall. These results are compatible with the broader literature that emphasizes the role of emotional regulation, empathy, and perspective-taking in fostering forgiveness. McCullough et al.<sup>[25]</sup> highlights that in the absence of psychiatric conditions, forgiveness is a relatively stable interpersonal capacity.<sup>[25]</sup> Our findings reinforce this view by demonstrating that individuals without ADHD or ASPD showed consistently higher levels of forgiveness. Nevertheless, it is important to consider studies that report individual differences in forgiveness even among non-clinical populations. Cultural, situational, and personality-related factors may all influence forgiveness tendencies, which may explain some variability in our control group's scores. In line with this, a positive correlation was also observed between ADHD symptom scores and forgiveness within the control group. This suggests that, although subclinical, certain attentional or emotional traits may influence forgiveness behavior even in psychiatrically healthy individuals. However, since the control group did not meet criteria for any psychiatric diagnosis, this association should be interpreted as a reflection of normative individual variability, rather than as an indicator of underlying pathology.

Taken together, our results support the hypothesis that forgiveness should not be interpreted as a straightforward indicator of personality or moral integrity, particularly in populations where comorbid ADHD may influence interpersonal functioning. The observed positive association between ADHD symptoms and forgiveness in ASPD individuals underscores the potential for diagnostic overlap. Clinicians should consider that a forgiving disposition may stem from ADHD-related emotional impulsivity rather than the absence of antisocial tendencies. This complexity requires multidimensional assessment strategies and highlights the importance of distinguishing between ADHD and ASPD in clinical evaluation and treatment planning.

Despite the strengths and originality of this study, several limitations should be acknowledged. First, the cross-sectional nature of the design prevents causal conclusions from being drawn regarding the relationship between ADHD symptoms and forgiveness behavior. Second, although ADHD diagnoses in the clinical groups were established through psychiatric evaluation and supported by symptom scale scores, forgiveness was assessed solely through self-report measures. This may introduce bias, particularly in individuals with antisocial traits who may underreport or misrepresent their interpersonal behaviors. Furthermore, while healthy individuals were included as a control group, it is possible that subtle or undiagnosed psychiatric characteristics may not have been fully ruled out. The cultural context in which forgiveness is interpreted and expressed may also influence the findings and limit their generalizability to broader or cross-cultural populations. Future research should consider longitudinal designs, multimodal assessment strategies, and broader sample diversity to further validate and expand upon these results.

## CONCLUSION

In conclusion, this study contributes to a nuanced understanding of how ADHD symptoms interact with antisocial traits to influence forgiveness behavior. The results suggest that forgiveness should not be used as a standalone indicator of moral or personality functioning, particularly in individuals with possible comorbidities. Differentiated assessment and treatment approaches are essential for accurately identifying and addressing the emotional and behavioral needs of these complex clinical populations.

### Ethics Committee Approval

The study was approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee (Date: 12.10.2018, Decision No: 2018/514/139/1).

### Informed Consent

Retrospective study.

### Peer-review

Externally peer-reviewed.

### Conflict of Interest

None declared.

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## Antisosyal Kişilik Bozukluğunda Dikkat Eksikliği Hiperaktivite Bozukluğu Belirtileri ile Affedicilik Davranış Paterninin İlişkisi

**Amaç:** Bu çalışma, Dikkat Eksikliği ve Hiperaktivite Bozukluğu (DEHB) belirti şiddeti ile Affetme davranışı arasındaki ilişkiyi, Antisosyal Kişilik Bozukluğu (ASKB) tanısı olan bireylerde – DEHB eş tanımlı olanlar ve olmayanlar – ile sağlıklı kontrol grubu arasında karşılaştırmalı olarak incelemeyi amaçlamıştır.


**Gereç ve Yöntem:** Çalışma örneklemini, üç gruba ayrılmış toplam 190 erkek katılımcıdan oluşmaktadır: DEHB belirtileri gösteren ASKB bireyleri (n=52), DEHB belirtisi göstermeyen ASKB bireyleri (n=38) ve sağlıklı kontrol grubu (n=100). Tanılar, DSM-V-TR kriterlerine dayalı yapılandırılmış klinik görüşmelerle konulmuştur. Katılımcılar, Yetişkin DEHB Belirti Ölçeği ve Affetme Ölçeği'ni doldurmuştur. Her grup için ayrı ayrı korelasyon analizleri yapılarak DEHB belirti puanları ile affetme arasındaki ilişki incelenmiştir.

**Bulgular:** Sosyodemografik değişkenler tüm gruplarda eşit şekilde dağılmıştır. DEHB belirtisi olmayan ASKB grubunda DEHB belirtileri ile affetme arasında anlamlı negatif bir korelasyon saptanmıştır ( $r=-0.418$ ,  $p=0.008$ ); bu durum, bu grupta artan DEHB belirtilerinin daha düşük affetme ile ilişkili olduğunu göstermektedir. Buna karşılık, DEHB belirtileri olan ASKB grubunda ( $r=0.104$ ,  $p=0.043$ ) ve sağlıklı kontrol grubunda ( $r=0.196$ ,  $p=0.005$ ) pozitif korelasyonlar bulunmuştur; bu gruplarda artan DEHB belirtilerinin daha yüksek affetme eğilimiyle ilişkili olabileceğini göstermektedir.

**Sonuç:** Bulgular, DEHB belirtilerinin, antisosyal özelliklere sahip bireylerde bile duygusal tepki verme ve affetme davranışını etkileyebileceğini göstermektedir. Antisosyal bireylerde gözlenen affediciliğin, antisosyal patolojinin yokluğundan çok, DEHB'ye bağlı duygusal değişkenlikten kaynaklanabileceği düşünülmektedir. Bu sonuçlar, DEHB ve ASKB arasındaki tanısal karmaşıklığı vurgulamakta ve klinik uygulamada çok boyutlu değerlendirmenin önemini ortaya koymaktadır.

**Anahtar Sözcükler:** Affedicilik; antisosyal kişilik bozukluğu; dikkat eksikliği ve hiperaktivite bozukluğu.

# Potential Immunomodulatory Role of IL-37<sup>+</sup>CD4<sup>+</sup> Helper T Cells in Autoimmune Hepatitis

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**Keywords:** Autoimmune  
hepatitis; helper T cell; IL-37;  
Ishak scoring.



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## ABSTRACT

**Objective:** Autoimmune hepatitis (AIH) is a chronic liver disease characterized by inflammation of unknown origin. It is marked by high levels of immunoglobulin G (IgG) and autoantibodies in the blood. Pathologically, AIH shows infiltration of inflammatory cells, particularly plasma cells, and signs of interface hepatitis. The role of a specific type of CD4<sup>+</sup> helper T cells, which produce interleukin (IL)-37, has been established in autoimmune diseases. However, their role in AIH is still not well understood. To shed light on this, our study aimed to investigate the gene and protein expression of IL-37 in liver biopsies of AIH patients and determine the involvement of tissue-resident IL-37-producing helper T cells in the development of AIH.

**Methods:** We conducted a comparative study involving 20 patients diagnosed with AIH and 17 healthy individuals as controls. IL-37 gene expression was measured using quantitative real-time polymerase chain reaction (qRT-PCR), and immunofluorescence double staining was performed to identify IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells in the liver tissue. The ratio of IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells among total inflammatory cells was calculated to assess their abundance in AIH patients.

**Results:** Our findings revealed a significant increase in the ratio of IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells in patients with AIH ( $p < 0.05$ ). Additionally, IL-37 gene expression was upregulated in AIH patients ( $p < 0.01$ ). Importantly, the ratio of IL-37<sup>+</sup>CD4<sup>+</sup> Th cells showed a negative correlation with the severity of portal inflammation and Ishak scoring.

**Conclusion:** Our results highlight IL-37-producing helper T cells may be potential therapeutic targets for autoimmune hepatitis. Further studies are warranted to elucidate their precise mechanisms and therapeutic implications.

## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic liver disorder mediated by immunity that may develop into liver fibrosis.<sup>[1]</sup> The pathophysiology of AIH is influenced by CD8<sup>+</sup> T cell

cytotoxicity, autoantibodies made by B cells,<sup>[2]</sup> unique genetic characteristics,<sup>[3]</sup> and compromised immunological systems such as CD4<sup>+</sup> T cells<sup>[4]</sup> and Treg cells.<sup>[5]</sup> Damage to the liver results from the disturbance of the equilibrium between Treg cells and effector cells, which leads to the

development of the autoinflammatory response.<sup>[6]</sup> Treg cells offer immunotolerance by limiting the proliferation, cytokine production, and cytotoxicity of effector cells.<sup>[7]</sup> A progressive necro-inflammatory, fibrotic process results from the T cell-mediated immune system attacking liver antigens when this immunological tolerance is weakened.<sup>[8]</sup> AIH is diagnosed histologically using interphase hepatitis, increased serum immunoglobulin G (IgG) levels, and the presence of autoantibodies. Additionally, the efficacy of therapy and post-treatment remission are tracked using these markers.<sup>[4]</sup> Currently, azathioprine and prednisone are used to treat AIH. These combination therapies are used to lessen the side effects of prednisone or steroids taken alone, and they are effective in 80–90% of patients.<sup>[9]</sup> Since there is no full cure for pharmacological therapy, the major objectives of treatment are to manage liver inflammation, produce biochemical remission, alleviate and/or reduce symptoms, halt the disease's development, assist in fibrosis regression, and minimize drug-related adverse effects.<sup>[3]</sup>

A member of the IL-1 cytokine family, human interleukin-37 (IL-37) was discovered lately. Despite being identified *in silico* in 2000, IL-37's anti-inflammatory effects were just recently identified.<sup>[10]</sup> Nold et al.<sup>[11]</sup> claim that IL-37 is special in that it lowers inflammation by reducing the synthesis of cytokines that promote inflammation. IL-37 is abundantly expressed in humans. Through its ability to block the production of many inflammatory cytokines, IL-37 plays a significant role in both innate and adaptive immune responses. IL-37 controls the expression of cytokines, cell division, metabolism, and transcription of genes.<sup>[11]</sup> Outside the cell, it suppresses the synthesis of IFN and lessens signal transmission through toll-like receptors, acting as an immunosuppressive drug.<sup>[12]</sup> Also, the autoimmune disorders of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) have been linked to IL-37.<sup>[13]</sup> Hepatocytes, cholangiocytes, and invading immune cells are the primary cell types that express IL-37. Kupffer cells, hepatic stellate cells, and Treg cells were all found to be positive for IL-37.<sup>[14]</sup> Hepatic fibrosis, the quantity of invading immune cells, is positively correlated with IL-37 production. In a study performed on mice, IL-37 has been shown to have effects on prolonging survival, reducing liver damage, expression of early fibrosis markers, and liver fibrosis.<sup>[15]</sup>

Additionally, T-cell subsets, such as IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells, have been linked to the control of immunological responses and the preservation of immune tolerance in autoimmune disorders.<sup>[16]</sup> The etiology of autoimmune disease has been linked to the deregulation of various immune cell types. For instance, the suppressive lymphocytes known as regulatory T cells are essential for immunoregulation and immunological homeostasis maintenance.<sup>[17]</sup> However, it is yet unknown how specifically IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells contribute to the regulation of the development and severity of AIH. Understanding their probable function may offer insightful information about the immunopathogenesis of AIH and suggest new treatment targets.

## MATERIALS AND METHODS

This study was approved by the Ethical Committee of Kartal Dr. Lutfi Kırdar City Hospital, School of Medicine, University of Health Sciences-Türkiye (Date: 19.07.2023; No: 2023/514/254/25), and Informed Consent was obtained from all participants after the Helsinki Declaration.

### Patients

All subjects gave their informed permission in accordance with the Helsinki Declaration. Paraffin blocks were chosen randomly to obtain a total of 20 patients, and 17 healthy volunteers were chosen for this study. The following criteria had to be fulfilled by study participants. Individuals with an autoimmune hepatitis diagnosis must be at least eighteen years old and free of other liver conditions. Liver tissues that had been partially removed for other purposes were sampled for the control group.

### Clinical Evaluation

Our patients' liver function and autoimmunity test results were systematically scored. The AST/ALT ratio was scored as follows: Negative for a ratio less than 0.6, 1 for a ratio greater than 0.6, 2 for a ratio greater than 0.8, and 3 for a ratio greater than 1.0. GGT levels were scored as negative for values less than 85 U/L, 1 greater than 1 time 85 U/L, 2 for values greater than 2 times, and 3 for values greater than 3 times. For ALP, the scoring was negative for values less than 147 IU/L, 1 for values greater than one time 147, 2 for values greater than 2 times, and 3 for values greater than 3 times. Total Bilirubin, Albumin, and IgG levels were each scored according to their multiples of 1.2 mg/dl, 5.4 g/dl, and 16 g/l, respectively. Autoantibodies such as ANA, LKM, ASMA, and AMA were scored based on the number of positive results: 1 For one positive, 2 for two, and 3 for three. The Ishak index was scored according to the severity: Negative for none, 1 for mild, 2 for moderate, and 3 for marked. The evaluation results are presented in Figure 1.

### Immunofluorescent double staining

Paraffin block biopsy samples were prepared by cutting 4 µm-thick pieces for immunofluorescent staining. After deparaffinization, tissue samples were blocked with superblock and 3% peroxidase block solutions before being cooked under pressure in a 10% citrate-buffered solution to expose antigens. At 4 °C, samples were incubated with anti-IL-37b (ab153889, rabbit polyclonal antibody, 1:200; Abcam) and anti-CD4 (ab25804, mouse monoclonal antibody, 1:200; Abcam) antibodies. Following primary antibody incubation, samples were biotinylated before secondary antibody incubations were carried out. The streptavidin conjugate Qdot R 525 (Q10141MP, Life Technologies, Eugene, OR, USA) was used to measure green fluorescence. Strep avidin R phycoerythrin conjugate (S-3402, Sigma-Aldrich, St. Louis, MO, USA) was incubated for an hour at a dilution of 1:200 to produce red fluorescence. Hoechst 33342 (Thermo Scientific, 62249) was in-

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	
AST/ALT ratio (<0.6/>0.6/>0.8/>1.0)(Negative-score 3)																					
GGT (<85/>85/>170/>255 u/l) (Negative-score 3)																					
ALP (<147/>147/>294/>441 iu/l)(Negative-score 3)																					
Total Bilirubin (<1.2/>1.2/>2.4/>3.6 mg/dl)(Negative-score 3)																					
Albumin (<5.4/>5.4/>10.8/>16.2 g/dl)(Negative-score 3)																					
IgG (<16/>16/>24/>32 g/l)(Negative-score 3)																					
ANA (Negative/+ /++ /+++)																					
LKM (Negative/+ /++ /+++)																					
ASMA (Negative/+ /++ /+++)																					
AMA (Negative/+ /++ /+++)																					
Peace meal necrosis (None/Mild/Moderate/Marked)																					
Focal necrosis (None/Mild/Moderate/Marked)																					
Portal inflammation (None/Mild/Moderate/Marked)																					
Fibrosis (None/Mild/Moderate/Marked)																					
Ishak activity index (Mild/Moderate/Marked)																					
(Negative-score 3) or (Negative/+ /++ /+++)																					
or (None/Mild/Moderate/Marked)																					Not available

**Figure 1.** Clinical evaluation of the patients. The negative evaluation results were indicated in a very light gray, a score of 1 in light gray, a score of 2 in dark gray, and a score of 3 in the darkest shade of gray. Unavailable test results were marked in white. AST: Aspartate aminotransferase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; ANA: Antinuclear antibody; LKM: Anti-liver-kidney microsomal antibody; ASMA: Anti-smooth muscle antibody; AMA: Anti-mitochondrial antibody.

incubated for 5 min at a dilution of 1:2000 for core staining. For negative controls, the same procedure was followed, but no primary antibody. After the immunofluorescence staining, samples were investigated under an inverted fluorescent microscope (DMi 8S, Leica). Among all inflammatory cells, the proportion of immunofluorescent-labeled IL-37<sup>+</sup>CD4<sup>+</sup> T helper cells was examined.

### qRT-PCR

Quantitative real-time PCR (qRT-PCR) was performed to assess IL-37 mRNA expression in patient and control biopsy samples. Total RNA was extracted from FFPE tissues using tripleXtractor reagent (GRiSP, Portugal), and purity (A260/280=1.8–2.0) was verified spectrophotometrically. cDNA was synthesized from 500 ng RNA using the SCRIPT cDNA Synthesis Kit, followed by amplification with BlasTaq™ 2X MasterMix (abm) on a LightCycler® 480 (Roche). IL-37 and 18S rRNA primers were purchased pre-validated. Relative expression was normalized to 18S rRNA using the  $2^{-\Delta\Delta CT}$  method.<sup>[18]</sup>

### Histopathological studies

FFPE biopsy tissues were sliced into sections that were 4 μm thick. The Ishak scoring system was used to score the sections after they had been stained with hematoxylin and eosin (H&E), Masson Trichrome, Periodic acid–Schiff (PAS), diastase-PAS (D-PAS), and Reticulin. Ishak is a popular scoring system that provides an unbiased evaluation of liver inflammation in both clinical practice and research. The Ishak grading and staging were used to assess inflammation, necrosis, and fibrosis in liver biopsies. In the inflammation assessment, 0–4 corresponded to mild, 4–8 moderate, and 9–12 severe hepatitis. Ishak scoring, which ranged from 0 to 4 (and, for some parameters, from 0

to 6), was used to evaluate each parameter separately. A score of 0 indicated no inflammation at all, whereas a score of 4 indicated severe and widespread inflammation. These characteristics were used to rate each individual inflammation in the liver sample, and the final score was calculated. Similar to inflammation, a score of 0 indicated neither fibrosis nor necrosis, whereas a score of 6 indicated both fibrosis and significant necrosis. Moreover, the Ishak index contents were scored separately again according to the severity: Negative for none, 1 for mild, 2 for moderate, and 3 for marked. The evaluation results are presented in Figure 1 as well.

As for immunofluorescent staining evaluation, two doctors analyzed fluorescent staining images (20x). Each sample was photographed at 5 different hot spots of the liver. CD4<sup>+</sup>IL37<sup>+</sup> T cells were identified by their morphology and location, and the positive cells were counted manually.

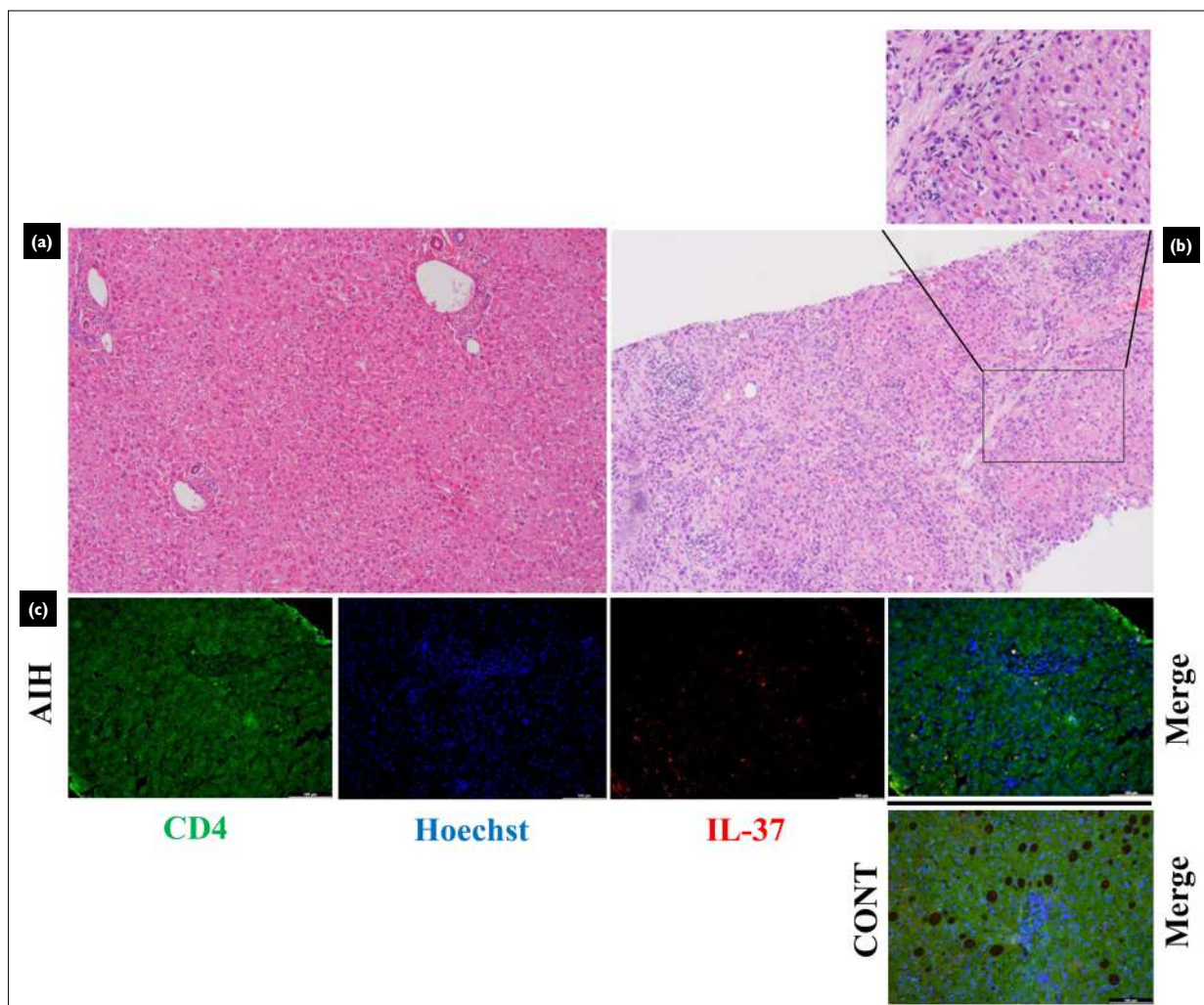
### Statistical Analysis

Data analysis methods were performed using the Mann-Whitney U test and Spearman's correlation test after Shapiro-Wilk analysis. P values less than 0.05 were used to determine statistical significance. The statistical software GraphPad Prism 8.1.1 was used for all analyses.

## RESULTS

### Clinical profiles of participants

The clinical characteristics of AIH patients and healthy controls are presented here. The mean age at diagnosis was 47.1 years, and there were 5/15 male to female patients with AIH. The following were the laboratory results at diagnosis: Total bilirubin (T-bil), 3.064–4.590 mg/



**Figure 2.** Histopathology of normal liver and AIH and immunofluorescent double staining of IL-37-producing helper T cells. **(a)** Normal liver (H&E; original magnification 10x). **(b)** Mononuclear inflammatory cells consisting of plasma cells, interphase hepatitis, and focal inflammation in the parenchyma were visible in the portal areas (H&E; original magnification 10x). Plasma cells in the portal area, periportal hepatocyte rosette formation, and emperipolesis were observed in the parenchyma. (Right upper corner image) (H&E; original magnification 40x). **(c)** Immunofluorescence double staining of IL-37/CD4 in AIH and CONT (Original magnification was 20x). AIH: CD4 (green); IL-37 (red); Hoechst (blue); Merge (yellow) (IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells signed in yellow arrow). Control: Merge (yellow). AIH for autoimmune hepatitis, CONT for control.

dl; AST, 287.1–318.6 U/l; ALT, 402.5–493.3 U/l; alkaline phosphatase (ALP), 152.1–99.4 U/l; gamma-glutamyl transferase (GGT), 123.9–95.6 U/l; and albumin, 21.84–19.68 g/dl. The grading of necroinflammatory activity was mild (8/20, 40%), moderate (9/20, 45%), and severe (3/20, 15%) according to the results of the Ishak grading and staging method. F0 (2/20, 10%), F1 (9/20, 45%), F2 (5/20, 25%), F3 (0/20, 00.0%), F4 (0/20, 00.0%), and F5 (4/20, 20%) were the stages of fibrosis. In control, the male/female ratio was 7/10, and the mean age at diagnosis was 55.6 years.

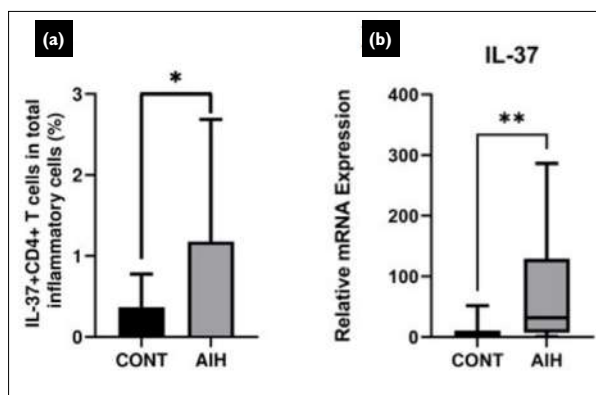
### Histopathological findings

In the normal control liver, no evident inflammation was found (Fig. 2A). In AIH patients, portal inflammation was observed to be mostly constituted of lymphocytes with

varying amounts of plasma cells (Fig. 2B). Plasma cell clusters were seen. The lobular alteration, which varied from patchy to confluent necrosis, was mostly caused by necrotic-inflammatory damage. Confluent necrosis and inflammation were visible in the perivenular region. It was connected to the typical peri-portal inflammation of the portal area. In several instances, bridging necrosis was also seen, which suggests that interphase hepatitis deeply penetrated the lobules.

### The number of IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells increased in the AIH

In samples from people with AIH and healthy controls, IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells were stained with anti-CD4 and anti-IL-37 antibodies (Fig. 2C). In all AIH biopsies, the



**Figure 3.** Proportion of IL-37-producing tissue-derived helper T cells in AIH versus relative mRNA expression of IL-37 in AIH. **(a)** Comparison of AIH and CONT IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells. When compared to the CONT group, the AIH group showed a larger ratio of double-positive IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells (AIH n=20 vs. CONT n=17, \*p<0.05). **(b)** AIH group's liver biopsy showed a significantly greater relative expression of IL-37 mRNA than the CONT group. (AIH n=20 vs. CONT n=15, \*\*p<0.01). AIH stands for autoimmune hepatitis; CONT stands for control.

ratio of IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells in total inflammatory cells was calculated. Contrary to the healthy control, IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells were considerably higher in the AIH (Median 0.725, range 0.474-1.884) vs. Control (Median 0.410, range 0.156-0.578), p=0.033) (Fig. 3A).

### In individuals with AIH, the relative mRNA expression of IL-37 increased

By using qRT-PCR, we assessed the levels of IL-37 gene expression in the AIH biopsies of patients who had been diagnosed with the disease, as well as in control biopsy samples to look into the potential function of IL-37 in AIH. Relative IL-37 mRNA expression in AIH was (Median 31.98, range 0.8138-286.58) (n=20), while it was (Median 4.573, range 0.0249-51.91) (n=15) in controls. When compared to the healthy control, AIH patients had considerably higher levels of IL-37 expression compared to the healthy control (p=0.0068) (Fig. 3B).

### Negative relationship between IL-37<sup>+</sup>CD4<sup>+</sup> helper T cell count and severity of portal inflammation and Ishak scoring of AIH

In the Spearman rank coefficient analysis, IL-37<sup>+</sup>CD4<sup>+</sup> helper T cell count was considerably negatively connected with the grading of inflammatory activity (r=-0.66, p=0.002) and negatively correlated with Ishak scoring (r=-0.51, p=0.026).

## DISCUSSION

The investigation's findings provide insight into the pathophysiology of AIH and the function of Th cells that release IL-37. AIH patients had a much-increased ratio of IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells, which suggests that these cells

may play a role in the disease-related immune response. This result was in line with previous studies that proposed the genesis and regulation of certain autoimmune diseases were mediated by immune cells that produced IL-37.<sup>[11]</sup> The idea that IL-37 could play a crucial role in regulating the inflammatory response in AIH was further reinforced by the fact that AIH patients had higher levels of IL-37 expression. The intriguing finding was that IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells were inversely connected to the degree of the disease. It suggested that in addition to its development, IL-37 might also play a reversal role in the onset, course, and severity of AIH.

IL-37 has been shown to have anti-inflammatory effects by blocking the action of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and interferon-gamma (IFN- $\gamma$ ).<sup>[10]</sup> IL-37 suppresses the sustained hepatic IFN- $\gamma$ /TNF- $\alpha$  production and T cell-dependent liver injury.<sup>[19]</sup> Immune cell infiltration and fibrosis in pediatric autoimmune liver diseases are correlated with IL-37 expression.<sup>[14]</sup> IL-37 likely acts as a negative immune response regulator, inhibiting the inflammatory cascade and promoting immunological tolerance in AIH. IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells are significantly present in the liver tissue of AIH patients, indicating that these cells actively trigger a localized immune response within the hepatic milieu. Tissue-derived helper T cells have been implicated in the pathogenesis and development of tissue-specific inflammation in autoimmune diseases.<sup>[5]</sup> The rise of IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells in the liver tissue suggested that the immune system was trying to balance the inflammatory milieu and return to immunological homeostasis. To precisely identify the mechanisms by which IL-37<sup>+</sup>CD4<sup>+</sup> helper T cells are drawn to and activated in the liver tissue of AIH patients, additional investigation is necessary.

Through the regulation of the inflammatory response and the restoration of immunological tolerance, strategies targeted at augmenting IL-37 expression or activity may have therapeutic implications for AIH. In preclinical models of various autoimmune disorders, therapeutic strategies that target IL-37 have demonstrated promise.<sup>[5,12]</sup> Developing targeted medicines or interventions to increase IL-37 production or strengthen its anti-inflammatory effects is required to study the therapeutic potential of IL-37 modulation in AIH.

### Limitations

This study had several limitations. First, due to its retrospective design, patients could not be followed or monitored in a standardized timeframe. Although all cases met the diagnostic criteria for AIH, histopathological findings varied in severity, ranging from mild to severe disease. The lack of synchrony in the timing of biochemical marker assessments further complicated data interpretation. Additionally, the sample size was smaller than anticipated. As this was a student-led project with limited funding, we were unable to perform certain immunofluorescent stains that could have provided further insights, such as

the Foxp3 regulatory T cells marker. In the future, we aim to conduct prospective studies with a larger cohort and more comprehensive data to better elucidate the pathogenesis of AIH.

## CONCLUSION

Our research demonstrated that patients with autoimmune hepatitis have significantly higher levels of IL-37 gene expression and IL-37<sup>+</sup>CD4<sup>+</sup> helper T cell proportions than healthy controls. Significantly, histological scoring and the degree of portal inflammation were adversely connected with the higher number of IL-37<sup>+</sup>CD4<sup>+</sup> T cells, indicating a possible protective or regulatory function in the course of the disease. These results point to helper T cells that produce IL-37 as possible treatment targets for autoimmune hepatitis. To clarify their exact mechanism and therapeutic implications, more research is necessary.

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## Ethics Committee Approval

The study was approved by the Ethical Committee of Kartal Dr. Lutfi Kırdar City Hospital, School of Medicine, University of Health Sciences (Date: 19.07.2023, Decision No: 2023/514/254/25).

## Informed Consent

Retrospective study.

## Peer-review

Externally peer-reviewed.

## Data availability statement

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

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## Authorship Contributions

Concept: S.T., L.I., N.B., G.Y., S.K., S.E., K.S., G.H.; Design: S.T., L.I., N.B., G.Y., S.K., S.E., K.S., G.H.; Supervision: S.E., S.K., G.H.; Materials: S.E., S.K., G.H.; Data collection &/or processing: S.E., S.K., G.H.; Analysis and/or interpretation: S.E., S.K., G.H., G.Y.; Literature search: S.T., L.I., N.B., G.Y., S.K., S.E., K.S., G.H.; Writing: G.H.; Critical review: S.T., L.I., N.B., G.Y., S.K., S.E., K.S., G.H.

## Conflict of Interest

None declared.

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## Otoimmün Hepatitte IL-37<sup>+</sup>CD4<sup>+</sup> Yardımcı T Hücrelerinin Potansiyel İmmünomodülatör Rolü

**Amaç:** Otoimmün hepatit (AIH), kökeni bilinmeyen inflamasyonla kendini gösteren kronik bir karaciğer hastalığıdır. Kanda yüksek immüno-globulin G (IgG) ve otoantikör seviyeleri ile karakterizedir. Patolojik olarak AIH, özellikle plazma hücreleri olmak üzere inflamatuvar hücrelerin infiltrasyonu ve arayüz hepatiti belirtileri gösterir. İnterlökin (IL)-37 üreten belirli bir CD4<sup>+</sup> yardımcı T hücresi tipinin otoimmün hastalıklardaki rolü belirlenmiştir. Ancak, AIH'deki rolleri henüz tam olarak anlaşılammıştır. Bu konuya ışık tutmak için çalışmamız, AIH hastalarının karaciğer biyopsilerinde IL-37 gen ve protein ekspresyonunu araştırmayı ve dokuda yerleşik IL-37 üreten yardımcı T hücrelerinin AIH gelişimindeki rolünü belirlemeyi amaçlamıştır.

**Gereç ve Yöntem:** AIH tanısı almış 20 hasta ve kontrol grubu olarak 17 sağlıklı bireyi içeren karşılaştırmalı bir çalışma yürüttük. IL-37 gen ekspresyonu, kantitatif gerçek zamanlı polimeraz zincir reaksiyonu (qRT-PCR) kullanılarak ölçüldü ve karaciğer dokusunda IL-37<sup>+</sup>CD4<sup>+</sup> yardımcı T hücrelerini tanımlamak için immünofloresan çift boyama yapıldı. AIH hastalarında IL-37<sup>+</sup>CD4<sup>+</sup> yardımcı T hücrelerinin toplam inflamatuvar hücreler arasındaki oranı hesaplanarak sayımları yapıldı.

**Bulgular:** Bulgularımız, AIH hastalarında IL-37<sup>+</sup>CD4<sup>+</sup> yardımcı T hücrelerinin oranında anlamlı bir artış olduğunu ortaya koydu ( $p < 0.05$ ). Ek olarak, IL-37 gen ekspresyonu AIH hastalarında artmıştır ( $p < 0.01$ ). Daha da önemlisi, IL-37<sup>+</sup>CD4<sup>+</sup> yardımcı T hücrelerinin oranı, portal inflamasyonun şiddeti ve Ishak skorlaması ile negatif korelasyon göstermiştir.

**Sonuç:** IL-37 üreten yardımcı T hücrelerinin otoimmün hepatit için potansiyel tedavi hedefleri olabileceğini vurgulamaktadır. Kesin mekanizmalarını ve tedavi edici etkilerini aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.

**Anahtar Sözcükler:** Otoimmün hepatit; IL-37; yardımcı T hücresi; Ishak skorlaması.

# Evaluation of Choroidal Vasculature Index and Choroidal Thickness in Newly Diagnosed Fibromyalgia Patients

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**Keywords:** Choroidal thickness; choroidal vasculature index; fibromyalgia.



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## ABSTRACT

**Objective:** This study aimed to analyze and compare the early choroidal vasculature index (CVI) and choroidal thickness (CT) values of newly diagnosed fibromyalgia (FM) patients and healthy subjects.

**Methods:** The participants in this study consisted of 24 female FM patients (study group) and 30 similarly aged female healthy subjects (control group). Only newly diagnosed FM patients were included in the study group. FM was diagnosed according to the American College of Rheumatology (ACR) 2010 classification criteria. Fibromyalgia Impact Questionnaire (FIQ) was used to assess the disease severity. CT values were measured at five points: Subfoveal, 750  $\mu\text{m}$  temporally, 1500  $\mu\text{m}$  temporally, 750  $\mu\text{m}$  nasally to the foveal center, 1500  $\mu\text{m}$  nasally to the foveal center (1500-N). CVI values were measured using the public domain ImageJ software for subfoveal and total choroidal areas.

**Results:** CT values in 1500  $\mu\text{m}$  nasal and temporal were statistically lower in the FM group ( $p < 0.05$ ). While 750  $\mu\text{m}$  nasal and temporal, subfoveal CT values were not statistically significantly different ( $p > 0.05$ ). There was no statistically significant difference between the groups in terms of subfoveal-CVI, ( $p > 0.05$ ) but total-CVI values were significantly higher in the FM group ( $p < 0.05$ ).

**Conclusion:** The thinner choroidal thickness in the nasal and temporal regions compared to the central area, preserved choroidal vasculature index in the subfoveal area, and overall increased CVI in these patients may indicate that choroidal vascular changes and thinning start from the peripheral choroidal area at early stages of FM.

## INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome that affects 2-8% of the world population, primarily women, and the age range is typically between 30 and 35 years.<sup>[1,2]</sup> FM is characterized by depression, anxiety, mood disorders, memory impairment, insomnia, fatigue, chronic musculoskeletal pain, muscle stiffness, joint stiffness, cognitive dysfunction, headaches, inability to carry out normal daily activities, and general sensitivity.<sup>[3,4]</sup> The central physiology changes in FM patients. It is known that FM leads to alterations in mono-aminergic neurotransmission, such as increased substance P and glutamate levels, and decreased norepinephrine and serotonin levels in the spinal cord. Altered activity of endogenous cerebral opioids and dopamine dysregulation has also been observed.<sup>[5]</sup> The pathophysiology of FM also involves genetic predisposition, autonomic nervous system abnormalities, neuroen-

doctrinal factors, oxidative stress, psychosocial and environmental changes.<sup>[6]</sup> Fibromyalgia persists due to central sensitization, characterized by increased neuronal activity and changes in pain processing pathways. Neuroinflammation also plays a crucial role in this process. One of the main characteristics of neuroinflammation is the activation of glial cells, including microglia and astrocytes, in the central nervous system. These cells produce pro-inflammatory cytokines and chemokines. They contribute to increased pain sensitivity and the development of allodynia.<sup>[7]</sup> FM can be associated with many ocular symptoms such as blurred vision, foreign body sensation and irritation. Scleritis, including the necrotizing form, reduced corneal sensitivity, and dry eye syndrome, has been reported accompanying fibromyalgia. In addition, researches have shown that FM patients have decreased retinal nerve fiber layer (RNFL), ganglion cell layer (GCL) thicknesses, and thinner corneal stromal nerves with diminished sub-basal plexus nerve

density.<sup>[9]</sup> Regarding choroidal thickness (CT) there are three conflicting studies in the literature. Ulusoy et al.<sup>[9]</sup> and Sevimli et al.<sup>[10]</sup> found decreased CT in FM patients, but Boquete et al.<sup>[11]</sup> found no significant difference in CT in FM patients.

The choroid is the pigmented and highly vascularized layer of the posterior segment, providing seventy percent blood supply of the retina. However, due to its anatomic location, it is challenging to obtain clear images of the choroid. The novel optical coherence tomography (OCT) technology, used with enhanced depth imaging (EDI) mode has enabled ophthalmologists to visualize the choroidal anatomy with accurate cross-sectional images of high quality.<sup>[12,13]</sup> Although CT is commonly used to determine choroidal changes, many factors such as blood pressure, age, diurnal variation, gender, axial length of the eye can affect the CT results. Therefore, the choroid vascularity index (CVI), which represents the ratio of the luminal/total choroidal area (LA/TCA ratio), is widely preferred as a more reliable assessment method of choroid. CVI is not influenced by physiologic factors, and provides the opportunity to evaluate both LA and (SA) separately.<sup>[14]</sup>

The choroidal effect of fibromyalgia remains controversial. But it is known that neuroinflammation, an important mechanism in the pathogenesis of fibromyalgia, involves vascular changes.<sup>[7]</sup> Our goal is to contribute to the literature by analyzing the CVI and CT values of newly diagnosed FM patients before receiving treatment, and comparing with healthy subjects.

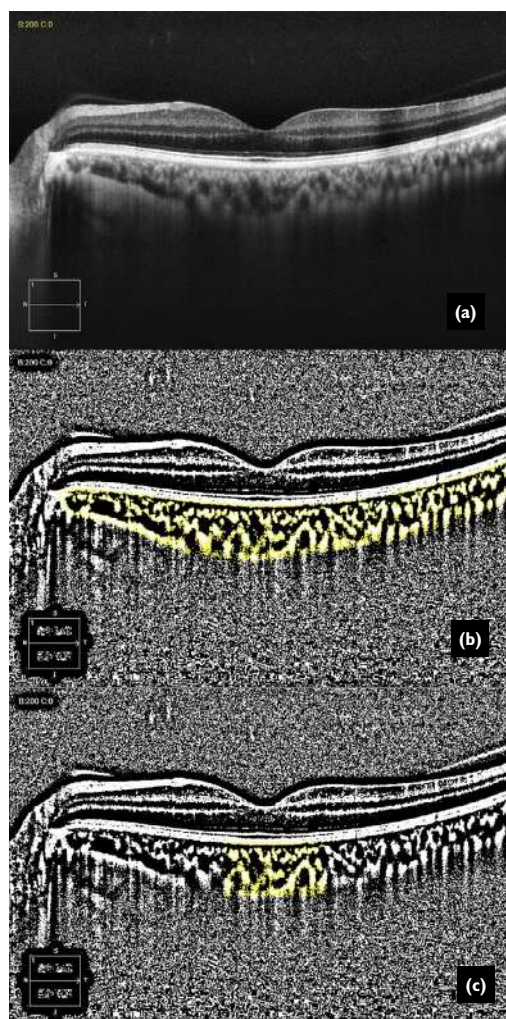
## MATERIALS AND METHODS

This cross-sectional, prospective study was performed between January 2023-December 2023, and approved by the Ethics Committee of Biruni University Hospital (No: 2022/71-04, Date: 24/06/2022) and it complies with the Declaration of Helsinki. The participants in this study consisted of 24 female FM patients (study group) and 30 similarly aged female healthy subjects (control group). Control group consists of healthy individuals without FM. Only newly diagnosed FM patients were included in the study group. Written consent was obtained from all participants. FM was diagnosed according to the American College of Rheumatology (ACR) 2010 classification criteria at the Physical Therapy and Rehabilitation clinic of our hospital. Widespread pain index (WPI) 3 – 6 and severity score (SS)  $\geq 9$  or WPI  $\geq 7$  and a SS  $\geq 5$  was defined as FM.<sup>[15-17]</sup>

Fibromyalgia Impact Questionnaire (FIQ) was used to assess the disease severity of FM patients.<sup>[18]</sup> The FIQ was preferred for its good sensitivity in demonstrating therapeutic effects, credible construct validity, and reliable test-retest reliability in FM patients.<sup>[19]</sup> The FIQ evaluates 10 areas: Sleep, stiffness, pain, occupational status, physical impairment, general well-being, work, fatigue/tiredness, depression, and anxiety on a scale of 0 to 100 points. Higher scores indicate a greater impact on the patient's life. We utilized the reliable and validated Turkish version

of the FIQ.<sup>[20]</sup> In this study, the FM patients were divided in two subgroups: Those with FIQ  $\geq 60$  were considered as severe FM group and those with FIQ  $< 60$  were considered as mild-moderate FM group. Severe FM group consist of 14 patients, and mild moderate FM group consist of 10 patients.

Participants with a history of medical treatment, cognitive impairment, other rheumatological diseases, best-corrected visual acuity (BCVA) worse than 20/20, any ocular diseases (uveitis, trauma, cataract, glaucoma, retinal diseases, etc.), a refractive error of  $\geq \pm 2.00D$  to avoid the effect of axial length on CT, previous laser or intravitreal injections, history of ocular surgery, systemic diseases (hypertension, vasculitis, heart disease, diabetes, neurological diseases, etc.) were excluded. Neurodegenerative diseases and obstructive sleep apnea syndrome (OSAS) were also excluded due to their potential effect on the visual system



**Figure 1.** The original and binarized macular enhanced depth imaging optic coherence tomography (EDI- OCT). Original EDI-OCT image (a); The binarized image used for calculating total CVI; dark pixels represent luminal area (LA), coloured pixels represent stromal area (SA)(b); subfoveal binarized image used for calculating subfoveal CVI: Dark pixels represent luminal area (LA), coloured pixels represent stromal area (SA) (c).

and choroid. Smoking was not taken into account in this study. However, participants who smoked, or consumed coffee or tea, were asked to wait for at least half an hour before the measurements were taken.

All participants underwent a detailed examination, including BCVA, slit lamp biomicroscope, applanation tonometry, and fundus examination. Subsequently, spectral domain optical coherence tomography (SD-OCT) was performed by the same experienced investigator between 08:00 and 10:00 a.m. to avoid diurnal variability. The investigator was blind to the FM diagnosis. The eye with the higher scan score index was chosen for OCT, and was used for statistical analyses.

Cirrus HD OCT-5000 device (Carl Zeiss, Jena, Germany) was used to measure the CT and CVI, with a single 9-mm horizontal EDI SD-OCT scan, based on an average of 100 images (Fig. 1). CT was measured manually measures from the outer edge of the retina pigment epithelium to the sclero-choroid interface. Measurements were taken at five points: Subfoveal, 750  $\mu$ m temporally to the foveal center (750-T), 1500  $\mu$ m temporally to the foveal center (1500-T), 750  $\mu$ m nasally to the foveal center (750-N), 1500  $\mu$ m nasally to the foveal center (1500-N). SA, LA, TCA and CVI were measured using the public domain ImageJ soft-

ware by Fiji (<http://fiji.sc/Fiji>) as previously described by Agrawal et al.<sup>[21]</sup> for both subfoveal (the choroid area between the nasal and temporal 750 microns from foveal center; subfoveal CVI) and total choroidal areas (full – length scan (total CVI)).<sup>[19]</sup> CT and CVI measurements were conducted by the same trained ophthalmologist.

The effect on optical parameters was determined by using the power analysis with the G\*Power program. When the value is taken as 1.0, it is detected for power: 0.85 (real power: 0.8507439) and type I error: 0.05. The minimum number of samples was determined n:23 for each group. Data analyze was performed using the IBM SPSS Statistics Version 21 Package Program in this study. The normal distribution of the variables was analyzed by Shapiro Wilk's Test, which indicated that the variables followed a normal distribution. Therefore, Independent T Test was used to analyze the differences between the groups. A p-value less than 0.05 was considered statistically significant. Pearson's correlation coefficient was used to establish the correlation between variables.

## RESULTS

There was no statistically significant difference in terms of age between the two groups (p=0.18) (Table I). 1500 – N

**Table 1.** Age comparison between groups

	n	Mean $\pm$ SD	Minimum age	Maximum age	p value
Fibromyalgia group	24	41.58 $\pm$ 11.45	21	60	0.188*
Control group	30	37.36 $\pm$ 11.61	18	59	

SDX Standard Deviation; n: number. \*Independent student's t test.

**Table 2.** Comparison of choroidal vascularity indexes and choroidal thicknesses between fibromyalgia and control group

	FM group (n=24)	Control group (n=30)	p value
	Mean $\pm$ SD ( $\mu$ m)	Mean $\pm$ SD ( $\mu$ m)	
1500 nasal-CT	262.20 $\pm$ 66.83	297.56 $\pm$ 44.72	0.032*
750 nasal-CT	311.87 $\pm$ 56.20	336.53 $\pm$ 49.67	0.098*
Subfoveal CT	366.58 $\pm$ 63.94	399.23 $\pm$ 55.13	0.054*
750 temporal-CT	331.33 $\pm$ 64.01	360.26 $\pm$ 44.65	0.076*
1500 temporal-CT	303.79 $\pm$ 64.73	336.36 $\pm$ 44.38	0.042*
Subfoveal-CVI	0.66 $\pm$ 0.01	0.65 $\pm$ 0.02	0.621*
Total-CVI	0.65 $\pm$ 0.01	0.63 $\pm$ 0.01	0.022*
Subfoveal-LA	0.34 $\pm$ 0.06	0.34 $\pm$ 0.08	0.945*
Subfoveal-SA	0.17 $\pm$ 0.03	0.17 $\pm$ 0.04	0.902*
Subfoveal-TCA	0.52 $\pm$ 0.10	0.52 $\pm$ 0.13	1.000*
Total-LA	1.48 $\pm$ 0.24	1.65 $\pm$ 0.29	0.020*
Total-SA	0.78 $\pm$ 0.12	0.9 $\pm$ 0.16	0.002*
Total-TCA	2.26 $\pm$ 0.35	2.53 $\pm$ 0.43	0.016*

SD: Standard Deviation; n: Number; CT: Choroidal thickness; CVI: Choroidal vascularity index; LA: Luminal area; SA: Stromal area; TCA: Total choroidal area. \*Independent student's t test.

**Table 3.** Comparison of choroidal vascularity indexes and choroidal thicknesses between severe FM and mild-moderate FM group

	Severe FM Group (n=14)	Mild-moderate FM Group (n=10)	p value
	Mean±SD (µm)	Mean±SD (µm)	
1500 nasal-CT	260.64±62.39	264.40±76.03	0.899*
750 nasal-CT	308.14±53.38	317.10±62.48	0.718*
Subfoveal CT	368.35±65.54	364.10±65.05	0.876*
750 temporal-CT	335.35±63.50	325.70±67.73	0.660*
1500 temporal-CT	307.35±55.60	298.80±78.71	0.772*
Subfoveal-CVI	0.65±0.01	0.66±0.02	0.158*
Total-CVI	0.65±0.01	0.64±0.01	0.102*
Subfoveal-LA	0.33±0.06	0.35±0.07	0.489*
Subfoveal-SA	0.17±0.03	0.17±0.03	0.900*
Subfoveal-TCA	0.51±0.10	0.53±0.10	0.607*
Total-LA	1.47±0.23	1.49±0.26	0.875*
Total-SA	0.76±0.13	0.81±0.11	0.390*
Total-TCA	2.24±0.36	2.30±0.36	0.689*

SD: Standard Deviation; n: Number; CT: Choroidal thickness; CVI: Choroidal vascularity index; LA: Luminal area; SA: Stromal area; TCA: Total choroidal area. \*Independent student's t test.

CT and 1500 – T CT values were statistically lower in the FM group than in the control group ( $p < 0.05$ ). While 750 – N CT, subfoveal CT and 750 – T CT values were lower in the fibromyalgia group, there was no statistically significant difference between the groups ( $p > 0.05$ ). There was no statistically significant difference between the groups in terms of subfoveal-CVI, subfoveal TCA, subfoveal LA, and subfoveal SA ( $p > 0.05$ ).

Total-CVI values were significantly higher in the FM group than in the control group ( $p < 0.05$ ). However, Total-LA, Total-SA, and Total-TCA values were lower in the FM group than in the control group, and these differences were statistically significant ( $p < 0.05$ ). The comparison of all these values is presented in (Table 2).

The evaluation of choroidal measurements between severe (n:14) and mild-moderate (n:10) FM patients is detailed in (Table 3). No statistical difference was found in terms of the CV and CVI values between these two subgroups. There was no correlation observed between FIQ score and choroidal variables in FM group.

## DISCUSSION

This study demonstrates the early changes of CT and CVI in newly diagnosed FM patients, and compares the results with the literature.

Ulusoy et al.<sup>[9]</sup> concluded that CT values decrease in FM patients due to alterations in autonomic nervous system functioning and correlated with disease activity. Sevimli et al.<sup>[10]</sup> also found thinner CT in FM patients, in their study based on the average CT at subfoveal 1500 µm. In contrast, Boquete et al.<sup>[11]</sup> found no significant differences in

any part of the choroid in FM patients and observed no correlation with disease severity. Boquete et al.<sup>[11]</sup> calculated CT in nine areas and obtained 64 measurements around the macula measured using the artificial intelligence. Therefore, they asserted that their results were more reliable. In our study, we observed that CT values were thinner in FM patients compared to healthy subjects in the areas 1500 µm temporally to the foveal center and 1500 µm nasally to the foveal center. Subfoveal, 750 µm nasally, and 750 µm temporally CT were also thinner in the fibromyalgia group, but this was not statistically significant. Additionally, CT values did not differ with FIQ score. Our sample group comprises fibromyalgia patients in the early stages of the disease. We speculate that CT thinning may start at the peripheral area in FM patients. Choroid is supplied by a rich vasoactive autonomic nerve with the parasympathetic muscarinic and sympathetic adrenergic receptors. Sympathetic hyperactivity leads to vasoconstriction and endothelial dysfunction via alpha-1 receptor stimulation. Studies showed that chronic hypertension, chronic heart failure and coronary artery disease patients have thinner choroid due to vasoconstriction. Autonomic nervous system fluctuations such as increased sympathetic hyperactivity may result with endothelial dysfunction and choroidal thinning in FM.<sup>[22-25]</sup>

Sevimli et al.<sup>[10]</sup> significantly higher total CVI values in FM patients. In their study, it is not specified from which area of the subfoveal region of OCT section the CVI measurement was taken. We also found higher total-CVI values in FM patients compared to healthy subjects. Differently we evaluated subfoveal-SA, subfoveal-LA, subfoveal-TCA, and subfoveal-CVI. These findings did not differ between FM

group and control subjects. However, we observed lower total-SA, total-LA, and total-TCA values in FM patients, along with higher total-CVI values compared to healthy subjects. Also, choroidal thinning might initially manifest in the peripheral region in early stages of FM. However, the decrease in SA is more pronounced than LA. This results in higher CVI values in the total area. Bambo et al.<sup>[26]</sup> examined the optic nerve head by colorimetric analysis software in FM patients, and revealed decreased hemoglobin levels. But they did not assess the macular area. In their OCT angiography study Garcia-Martin et al.<sup>[27]</sup> suggested that FM patients and healthy individuals has similar blood vessel density in the macular area. But superior sector vascular density had an inverse correlation with disease duration. Likewise, Öztürk et al.<sup>[28]</sup> found no significant differences in terms of superficial and deep capillary plexus densities, foveal avascular zone characteristics and, choriocapillaris flow area between FM patients and healthy controls. Sympathetic and neurotransmitter dysregulations such as acetylcholine and dopamine, and neurodegeneration may contribute to CVI changes in FM patients. Oxidative stress and neurodegeneration may be responsible of decrease in SA.<sup>[10,29]</sup> These findings are particularly consistent with the decrease in SA observed in our study.

Our participants are newly diagnosed FM patients, and exclusion criteria is very strict. Therefore, it is an opportunity to observe the early changes on choroid in FM patients. We assert that choroidal changes start at the peripheral area of the choroid in FM patients, and these changes are mostly about SA.

We did not find any significant difference in CT and CVI values between the severe FM and mild-moderate FM groups. Longitudinal studies or studies with larger sample sizes may reveal predictive associations between choroidal structural changes and FM severity.

The first limitation of our study is the inclusion of only female subjects. FM is more common in women than in men due to the altered responses to pain, menstrual cycle-related central nervous system input and higher levels of depression and anxiety.<sup>[29]</sup> Additionally, there are several studies in the literature that focus on female subjects with FM.<sup>[30-32]</sup> The second limitation is the relatively small sample size. We only included newly diagnosed FM patients before their treatment started, and our exclusion criteria were broad.

## CONCLUSION

Our study revealed that CT is thinner in FM patients at 1500 µm temporally and 1500 µm nasally to the foveal center, but no significant differences were observed at 750 µm temporally and 750 µm nasally to the foveal center, as well as in the subfoveal region. No significant difference was found in terms of subfoveal CVI between FM patients and healthy controls; however total CVI values were higher in FM group. Total LA, SA, and TCA values were lower in FM group. This suggests that the loss in stromal and vascular

area begins in the peripheral region of the choroid. Moreover, the reduction in stromal area of the choroid is more pronounced than that in the vascular area. The subfoveal area does not appear to be affected in FM. Studies with larger sample sizes are necessary to establish a more accurate association between choroidal parameters and FM.

## Ethics Committee Approval

The study was approved by the Ethics Committee of Biruni University Hospital (Date: 24.06.2022, Decision No: 2022/71-04).

## Informed Consent

Written consent was obtained from all participants.

## Peer-review

Externally peer-reviewed.

## Authorship Contributions

Concept: B.I., M.G.E.; Design: B.I., O.K.; Supervision: B.I., M.G.E., M.S.; Fundings: M.G.E., B.I.; Materials: M.S., B.I.; Data collection &/or processing: B.I., O.K., M.G.E.; Analysis and/or interpretation: B.I., M.S.; Literature search: B.I., M.G.E.; Writing: B.I., M.S.; Critical review: B.I., M.G.E., O.K., E.B.S.

## Conflict of Interest

None declared.

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## Yeni Tanı Alan Fibromyalji Hastalarında Koroid Vaskülarite İndeksi ve Koroid Kalınlığının Değerlendirilmesi

**Amaç:** Bu çalışmada yeni tanı alan fibromyalji (FM) hastaları ile sağlıklı bireylerin erken koroid vaskülarite indeksi (KVI) ve koroid kalınlığı (KK) değerlerinin analiz edilmesi ve karşılaştırılması amaçlandı.

**Gereç ve Yöntem:** Bu çalışmaya 24 kadın FM hastası (çalışma grubu) ve benzer yaşta 30 sağlıklı kadın gönüllü (kontrol grubu) dahil edildi. Çalışma grubuna sadece yeni tanı almış FM hastaları dahil edildi. FM tanısı Amerikan Romatoloji Koleji'nin (ARK) 2010 sınıflandırma kriterlerine göre konuldu. Hastalığın şiddetini değerlendirmek için Fibromyalji Etki Anketi (FEA) kullanıldı. KK değerleri beş noktada ölçüldü: Subfoveal, 750 µm foveal merkezin temporalı, 1500 µm foveal merkezin temporalı, 750 µm foveal merkezin nazalı, 1500 µm nazal olarak foveal merkezin nazalı. KVI değerleri, subfoveal ve toplam koroid alanları public domain ImageJ yazılımı kullanılarak ölçüldü.

**Bulgular:** 1500 µm nazal ve temporal KK değerleri FM grubunda istatistiksel olarak daha düşüktü ( $p < 0.05$ ). 750 µm nazal ve temporal, subfoveal KK değerlerinde ise istatistiksel olarak anlamlı fark yoktu ( $p > 0.05$ ). Subfoveal-KVI açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu ( $p > 0.05$ ), ancak total-KVI değerleri FM grubunda anlamlı olarak yüksekti ( $p < 0.05$ ).

**Sonuç:** Nazal ve temporal bölgelerdeki koroid kalınlığının santral bölgeye göre daha ince olması, subfoveal bölgedeki koroid vaskülarite indeksinin korunmuş olması ve bu hastalarda genel olarak artmış KVI, koroidal vasküler değişikliklerin ve incelenen erken dönemde FM hastalarında periferik koroid alanından başladığını gösterebilir.

**Anahtar Sözcükler:** Fibromyalji; koroid kalınlığı; koroid vaskülarite indeksi.

# The Role of the Albumin-Bilirubin Score in Predicting Hemolysis, Elevated Liver Enzymes, and Low Platelet Count Syndrome

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**Keywords:** ALBI score; ges-  
tational hypertension; HELLP  
syndrome; liver disease;  
preeclampsia; pregnancy  
hypertension.



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## ABSTRACT

**Objective:** This study evaluated the utility of the Albumin-Bilirubin (ALBI) score as an indicator of liver dysfunction during pregnancy. The aim was to investigate the effectiveness of the ALBI score, which assesses liver function, in predicting the development of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.

**Methods:** This retrospective case-control study was conducted at a tertiary center in Ankara between January 1, 2018, and January 1, 2022. Sixty-one patients diagnosed with HELLP syndrome and 122 healthy pregnant women, matched for age and gestational age, were included. Blood samples were collected at 20–28 weeks' gestation, an average of six weeks before the development of HELLP syndrome findings. Demographic, clinical, and biochemical data for all participants were analyzed. The ALBI scores of patients with confirmed HELLP syndrome were compared with those of the control group using regression and receiver operating characteristic (ROC) curve analysis to assess predictive value.

**Results:** Total bilirubin levels were significantly higher and albumin levels were significantly lower in the HELLP group ( $p < 0.05$ ). Consequently, ALBI scores were significantly higher ( $p = 0.004$ ). ROC showed that ALBI had discriminatory power in predicting HELLP syndrome (area under the curve = 0.629;  $p = 0.007$ ). In both the HELLP group and the group including all participants, the ALBI score was not statistically significant in predicting poor composite neonatal outcome ( $p > 0.05$ ).

**Conclusion:** Although the ALBI score is used in prognostication for liver diseases, it can also be used for early prediction of HELLP syndrome. Prospective multicenter studies are needed to confirm cutoff values and reliability.

## INTRODUCTION

HELLP syndrome is a complex, pregnancy-specific disease with systemic involvement, and its pathogenesis is not completely understood. However, it is assumed that trophoblast infiltration during placental formation and remodeling of the uterine spiral arterioles are closely associated with the development of the disease.<sup>[1]</sup> Preeclampsia and other hypertensive disorders are among the most serious complications of pregnancy and are the leading cause of direct maternal mortality, accounting for 27% of deaths.<sup>[2]</sup> In severe cases, multiple organ systems may be affected

and damaged, including the kidneys, liver, brain, and vascular system, increasing the risk of death. A severe form of preeclampsia in which liver function is impaired solely by pregnancy and is characterized by hemolysis, elevated liver enzymes, and low platelet count is known as HELLP syndrome.<sup>[3]</sup>

To date, various treatments and micronutrient supplements have been studied and proposed to reduce the risk of preeclampsia, including antiplatelet agents, antioxidant vitamins, vitamin D, calcium and magnesium supplements.<sup>[4,5]</sup> However, no treatment intervention or nutrient

supplementation has been proven effective for treating preeclampsia, which may result in catastrophic outcomes if appropriate management is delayed due to inadequate or ineffective screening methods or tools. As there is no proven prophylaxis or treatment for preeclampsia, the focus should be on early prediction and proper management of the at-risk group for the development of preeclampsia and HELLP syndrome. By investigating biomarkers linked to processes involved in the currently known etiopathogenesis of the disease, especially before clinical manifestation, significant progress can be made in the timely prediction of the disease, its severity, and prognosis. This allows for earlier initiation of therapeutic measures and intensive follow-up.

In women with preeclampsia, ischemic vascular changes and endothelial damage can be observed in all organs, especially the placenta, kidneys, brain, and liver. It has long been accepted that this systemic endothelial damage is caused by an imbalance between angiogenic and antiangiogenic factors, with the antiangiogenic side prevailing.<sup>[6]</sup> Liver histopathology of women with preeclampsia showed endothelial cell damage, microvesicular adiposity, fibrinogen accumulation and ischemic periportal hemorrhage.<sup>[7]</sup>

The albumin-bilirubin (ALBI) score was initially developed as a measure of hepatic function in hepatocellular carcinoma and was later successfully used to predict survival and prognosis in many non-malignant liver diseases.<sup>[8-10]</sup> Significant impairment of liver function is associated with high morbidity and mortality, regardless of the underlying cause. Therefore, ALBI, as a measure of hepatic function, may serve as a prognostic or predictive factor for conditions beyond primary liver diseases.

In this context, our hypothesis was based on the fact that the development of HELLP can be predicted by the ALBI score. Our aim was to investigate the efficacy of the ALBI score, which is used to measure liver function in various liver diseases, in predicting the development of HELLP syndrome in patients with preeclampsia.

## MATERIALS AND METHODS

### Design

We conducted a retrospective case-control study of women diagnosed with HELLP syndrome and healthy pregnant women between January 1, 2018, and January 1, 2022, at a large tertiary referral hospital in Ankara. After approval by the ethics committee of the local hospital for medical research (Date: 21/04/2022, No: E-90057706-799-05), the medical records were retrospectively reviewed. All procedures were conducted in accordance with ethical rules and the principles of the Declaration of Helsinki. However, as not all participants could be reached, and this was a retrospective study, written informed consent could not be obtained.

The age range of the pregnant women included in the study was 18-45 years. Patients with known cardiovascular, au-

toimmune, or endocrine disease, liver and gallbladder disease, acute or chronic kidney disease, known malignancies, malnutrition, multiple pregnancies, assisted reproductive technology pregnancies and smokers were excluded from the study. The diagnosis of HELLP was made according to the guidelines of the 2020 Practice Bulletin of the American College of Obstetricians and Gynecologists (ACOG).<sup>[11]</sup> The participants were divided into two groups: The study group included 61 patients diagnosed with HELLP syndrome, and the control group consisted of 122 healthy pregnant women matched for age and gestational week. A total of 183 cases were analyzed retrospectively.

### Randomization

Two patients – one before and one after each of the 61 retrospectively screened and verified patients with a HELLP diagnosis who presented to the hospital according to the hospital protocol number and met the inclusion and exclusion criteria – were included in the control group. The control group consisted of 122 individuals, with an allocation ratio of 1:2.

### Data collection

The demographic and clinical characteristics of the patients included in the study were analyzed in detail. Demographic data collected included age, body mass index (BMI), number of pregnancies, parity, previous pregnancy history, gestational age at presentation, gestational age at delivery, fetal sex, APGAR scores, need for neonatal resuscitation, neonatal characteristics, smoking status, and history of assisted reproductive treatment. Clinical data included patients' blood pressure readings and other clinical parameters specific to HELLP syndrome. Blood samples and laboratory data from patients diagnosed with HELLP syndrome were retrospectively analyzed using hospital records archived at the time of diagnosis.

Blood samples were collected between 20 and 28 weeks of gestation, before the diagnosis of HELLP syndrome (median time to diagnosis was 6 weeks). In the control group, blood samples were also collected between 20 and 28 weeks of gestation. The patients' laboratory parameters were analyzed comprehensively. Complete blood counts, including white blood cells, neutrophil granulocytes, lymphocytes, and platelets; biochemical analyses, such as aspartate aminotransferase, alanine transaminase, lactate dehydrogenase, albumin, and creatinine; bleeding profiles; and platelet function were measured. ALBI scores were calculated using the formula  $(\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$ .<sup>[7]</sup>

### CNO (composite neonatal outcome)

The composite neonatal outcome described fetal well-being and included several components: A 5-minute APGAR score above 7, no admission to a neonatal intensive care unit, and a birth weight over 2,500 g. The absence of these criteria or the presence of any adverse component was defined as "poor CNO".

**Table 1.** Maternal and neonatal demographic and clinical characteristics

Variable	Control (n=122)	HELLP (n=61)	p
Age (years)	26 (24-30)	29 (25-33)	0.055
BMI (kg/m <sup>2</sup> )	29.0 (26.1-32.9)	29 (26-33)	0.532
Gravida	2 (1-3)	2 (1-3)	0.922
Parity	1 (0-2)	1 (0-1)	0.581
Abortus	0 (0-0)	0 (0-1)	0.733
Gestational age at blood sampling (weeks)	26 (25-26)	26 (25-27)	0.945
Gestational age at delivery (weeks)	39 (38-40)	33 (29-35)	<b>&lt;0.001</b>
Fetal female gender	55 (45.1)	29 (47.5)	0.753
APGAR Score at 1st minute	9 (9-9)	7 (4-9)	<b>&lt;0.001</b>
APGAR Score at 5th minute	10 (10-10)	8 (7-10)	<b>&lt;0.001</b>
Neonatal intensive care unit admission	11 (9.0)	34 (55.1)	<b>&lt;0.001</b>
Birth weight (grams)	3240 (2948-3503)	1565 (847-2410)	<b>&lt;0.001</b>
Systolic blood pressure at birth (mmHg)	110 (106-111)	155 (150-160)	<b>&lt;0.001</b>
Diastolic pressure at birth (mmHg)	69 (66-71)	105 (98-110)	<b>&lt;0.001</b>
Poor composite neonatal outcome	16 (13.1)	49 (80.3)	<b>&lt;0.001</b>

BMI, body mass index. Data are expressed as median and quartiles (Q1-Q3), or number (percentage) where appropriate. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

### Statistical analysis

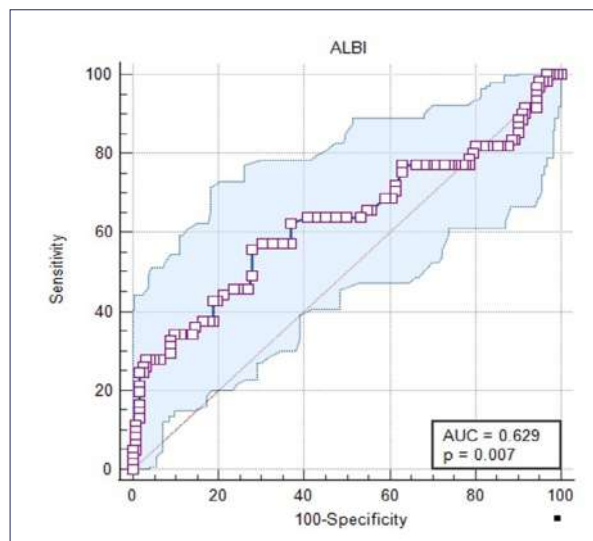
All statistical analyses were performed using RStudio (Af-fero General Public License v3; 2011). We used histograms, probability plots, and the Kolmogorov-Smirnov/Shapiro-Wilk tests to assess whether the variables were normally distributed. Descriptive analysis of non-normally distributed numerical data used medians and quartiles (Q1-Q3). Mann-Whitney U tests were conducted to compare these parameters among the groups. For categorical variables, descriptive analyses were presented as frequency and percentage. Relationships between categorical variables were analyzed using the Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) analysis was used to evaluate CNO and HELLP syndrome prediction parameters. When a cut-off value was significant, sensitivity, specificity, and area under the curve (AUC) were reported. Multivariate analysis used binary logistic regression to identify new independent HELLP syndrome variables from univariate analyses. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit statistic. A p-value below 0.05 indicated statistical significance.

### RESULTS

A total of 183 participants were included: 61 patients in the HELLP group and 122 in the control group. There were no significant differences between the groups in age, BMI, gravidity, parity, or history of miscarriage (all p>0.05). Gestational age at admission was similar (26 [25-26] weeks vs. 26 [25-27] weeks, p=0.945), but HELLP patients delivered significantly earlier (p<0.001). Neonatal outcomes were significantly worse in the HELLP group: 1st and 5th minute

APGAR scores were lower (p<0.001), the intensive care unit admission rate was higher (55.1% vs. 9.0%, p<0.001), birth weights were lower (p<0.001), and the rate of poor composite negative neonatal outcomes was higher (80.3% vs. 13.1%, p<0.001). Systolic and diastolic blood pressures were significantly higher in HELLP patients (p<0.001) (Table 1).

Hematologic parameters, including hemoglobin, leukocyte, neutrophil, monocyte, and platelet counts, were similar between groups, but lymphocyte counts were

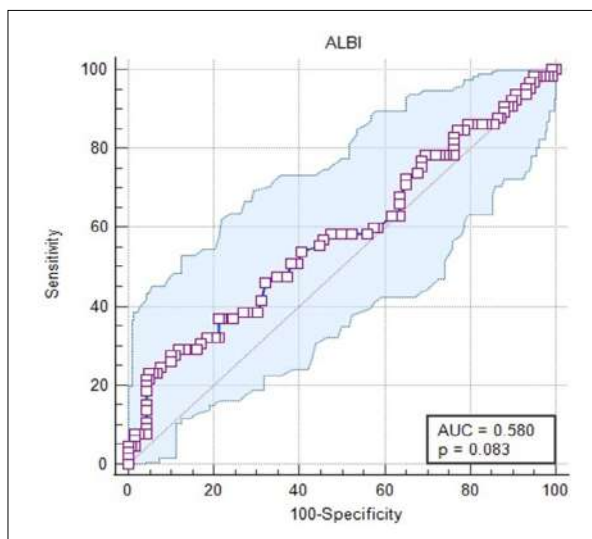


**Figure 1.** Receiver operating characteristic curve analysis of ALBI values for predicting hemolysis, elevated liver enzymes, and low platelet syndrome.

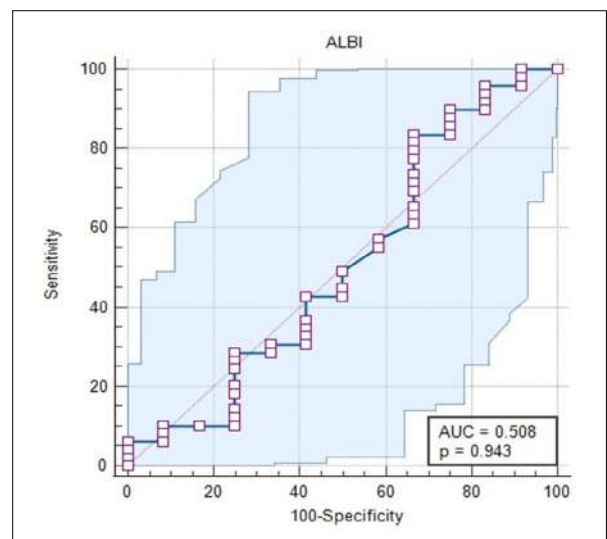
**Table 2.** Comparison of ALBI scores and laboratory parameters between groups

Variable	Control (n=122)	HELLP (n=61)	p
Hemoglobin (g/dL)	12.0 (11.0-12.8)	12.3 (11.2-13.2)	0.113
WBC (mm <sup>3</sup> )	8320 (7133-10018)	8900 (7095-10850)	0.478
Lymphocytes (mm <sup>3</sup> )	1825 (1500-2183)	2050 (1460-2830)	0.053
Neutrophils (mm <sup>3</sup> )	5705 (4668-7118)	5530 (4390-6920)	0.355
Monocytes (mm <sup>3</sup> )	600 (430-750)	630 (575-700)	0.105
Platelets (mm <sup>3</sup> )	247 (210-288)	273 (182-385)	0.253
AST (U/L)	15 (12-17)	16 (11-21)	0.240
ALT (U/L)	12 (10-16)	13 (9-18)	0.947
LDH (U/L)	199 (197-204)	200 (194-230)	0.502
Total bilirubin (mg/dL)	0.30 (0.23-0.42)	0.38 (0.27-0.52)	<b>0.018</b>
Albumin (g/L)	39.0 (37.7-41.0)	38.0 (35.0-42.0)	<b>0.012</b>
ALBI score	-2.84 (-3.04; -2.69)	-2.72 (-2.93; -2.36)	<b>0.004</b>

AST: Aspartate aminotransferase; ALBI: Albumin-bilirubin; ALT: Alanine transaminase; LDH; Lactate dehydrogenase; WBC: White blood count. Data are expressed as median and quartiles (Q1-Q3). A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.



**Figure 2.** Receiver operating characteristic curve analysis of albumin-bilirubin values for predicting poor composite neonatal outcomes in all participants.



**Figure 3.** Receiver operating characteristic curve analysis of albumin-bilirubin values for predicting poor composite neonatal outcomes in patients with hemolysis, elevated liver enzymes, and low platelet syndrome only.

slightly higher in the HELLP group ( $p=0.053$ ). Biochemical analysis showed significantly higher total bilirubin levels (0.38 [0.27–0.52] vs. 0.30 [0.23–0.42] mg/dL,  $p=0.018$ ) and lower albumin levels (38.0 [35.0–42.0] vs. 39.0 [37.7–41.0] g/L,  $p=0.012$ ) in the HELLP group, resulting in a higher ALBI score (-2.72 [-2.93; -2.36] vs. -2.84 [-3.04; -2.69],  $p=0.004$ ). No significant differences were found in AST, ALT, or LDH levels (Table 2). ROC analysis showed that the ALBI score had discriminatory power for HELLP, with an AUC of 0.629 (cut-off  $>-2.73$ ; 95% CI: 0.554–0.699;  $p=0.007$ ) (Fig. 1). At 90% sensitivity, the cut-off value was  $>-3.30$ , and at 90% specificity, it was  $>-2.58$ . The ALBI

score was not statistically significant for predicting poor CNO in patients diagnosed with HELLP or in the overall patient group ( $p=0.943$  and  $p=0.083$ , respectively) (Fig. 2 & Fig. 3). These results suggest that although the ALBI score provides moderate discrimination between HELLP patients and the control group, its utility for predicting adverse neonatal outcomes is limited (Table 3).

Table 4 examines the ALBI score calculated from blood samples taken at 20–28 weeks of gestation, maternal blood total bilirubin and albumin values, and demographic data as risk factors for the development of HELLP syndrome. Albumin and ALBI scores were statistically signif-

**Table 3.** ROC analysis for predicting HELLP syndrome (using the optimal cut-off, 90% sensitivity, and 90% specificity) and poor CNO using the ALBI score

Variable	AUC	CI 95%	p	Cut-off value	Sensitivity (%)	Specificity (%)
HELLP prediction	0.629	0.554-0.699	0.007	>-2.73	56	72
				>-2.58	34	90
				>-3.30	90	8
Poor CNO prediction in all participants	0.580	0.505-0.652	0.083	>-2.45	23	95
Poor CNO prediction only in HELLP group	0.508	0.376-0.638	0.943	>-3.12	84	33

ALBI: Albumin-bilirubin; AUC: Area under the curve; CI: Confidence interval; CNO: Composite neonatal outcome; HELLP: Hemolysis, elevated liver enzymes and low platelet; ROC: Receiver operating characteristic. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

**Table 4.** Multivariate and univariate logistic regression analyses to determine the increased risk of developing HELLP syndrome associated with changes in various parameters

Variable	OR	CI (95%)	p
Age (year)	1.048	0.992-1.106	0.094
BMI (kg/m <sup>2</sup> )	1.025	0.959-1.094	0.467
Parity	0.980	0.740-1.297	0.887
Albumin (g/L)	0.889	0.811-0.975	<b>0.012</b>
Total bilirubin (mg/dL)	5.119	0.878-29.850	0.070
ALBI	4.406	1.654-11.736	<b>0.003</b>
ALBI <sup>‡</sup>	5.102	1.861-13.984	<b>0.002</b>

ALBI: Albumin-bilirubin; BMI: Body mass index; CI: Confidence interval; HELLP: Hemolysis, elevated liver enzymes and low platelet; OR: Odds ratio. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. <sup>‡</sup>Age, BMI and parity adjusted.

icant (p<0.05). When ALBI scores were adjusted for age, BMI, and parity, each unit increase in the ALBI score increased the risk of developing HELLP syndrome by 5.102 times [OR: 5.102; 95% CI: 1.861–13.984; p=0.002].

## DISCUSSION

In this study, we investigated the diagnostic value of the ALBI score, which is calculated on the basis of albumin and bilirubin and provides information on liver function, in pregnant women with HELLP syndrome compared to healthy pregnant women. We showed that the ALBI score has a sensitivity of 90% for diagnosing HELLP syndrome when the cutoff value is set at -3.30. These biochemical changes were associated with prematurity, low birth weight, low APGAR scores, higher rates of ICU admission, and more frequent adverse neonatal outcomes, confirming the known burden of HELLP on perinatal health. Our findings were consistent with previous studies that reported liver dysfunction, endothelial damage, and systemic involvement in HELLP syndrome and preeclampsia, which are among the most severe pregnancy complications worldwide.<sup>[12-14]</sup>

The ALBI score was originally developed for the objective assessment of liver function in patients with hepatocellular carcinoma.<sup>[8]</sup> Since then, it has been validated as a predictor of morbidity and mortality in numerous non-malignant liver diseases.<sup>[15,16]</sup> In our study population, the ALBI score, with an AUC of 0.629, demonstrated moderate discriminatory power in distinguishing HELLP patients from controls. Although transaminase and lactate dehydrogenase (LDH) levels did not differ significantly between groups, the ALBI score detected subtle changes in liver function, demonstrating its potential as a more comprehensive index than individual liver markers.

In previous studies, the ALBI score was used to assess cholestasis in pregnancy and to investigate its association with liver damage. No difference was found between the control group and the cholestasis group regarding the ALBI score. However, unlike our study, the relationship between the ALBI score and pregnancy outcomes was not evaluated.<sup>[17,18]</sup> In our study, the predictive value of ALBI for neonatal outcomes was limited. Although HELLP syndrome was strongly associated with an unfavorable neonatal prognosis, ALBI did not significantly improve prediction of the composite neonatal outcome (AUC, 0.580). In

the analysis of the HELLP group, ALBI almost completely lost its prognostic ability (AUC, 0.508). These results suggest that although ALBI may be useful for detecting liver dysfunction and distinguishing a HELLP pregnancy from a healthy pregnancy, neonatal outcome is likely influenced by many additional maternal, fetal, and placental factors beyond liver function.

Currently, clinical studies support the validity of the ALBI score for assessing liver function during hepatectomy, radiofrequency ablation, transarterial chemoembolization, radiation therapy, and systemic therapy. However, because the ALBI score includes only serum albumin and bilirubin, it has limitations. First, serum albumin levels may vary in patients with liver disease, those receiving albumin replacement therapy, or those taking branched-chain amino acid medications. Second, albumin levels may differ depending on the measurement method used. Additionally, bilirubin levels may be elevated in patients with constitutional jaundice despite normal liver function, which can affect the ALBI score.<sup>[19]</sup> It should also be noted that the clinical presentation of HELLP syndrome does not arise primarily or solely from liver damage. However, despite these confounding factors, we believe that demonstrating a score obtained from a simple blood test can predict HELLP syndrome an average of six weeks before it occurs, which will inspire future studies. The ALBI score, considered significant for predicting preeclampsia.<sup>[20]</sup> has generally been supported by clinical studies and provides a valid basis for future research on bilirubin metabolism, liver inflammation, and immunology.

Our study has some limitations. First, generalizability may be limited by the single-center retrospective design. Second, we did not perform dynamic measurements of ALBI during pregnancy, which may have greater predictive value than a single measurement. Third, our sample size, particularly in the HELLP group, was relatively small, which may have reduced the statistical power of the ROC analysis.

## CONCLUSION

Despite these limitations, our results are clinically relevant. The ALBI score is a simple, inexpensive, and easy-to-calculate index based on routinely measured laboratory parameters. Its moderate ability to distinguish HELLP patients from healthy pregnancies suggests it could complement current diagnostic tools in clinical practice. However, its limited role in predicting neonatal outcomes highlights the need to integrate ALBI with other maternal, fetal, and placental biomarkers in future predictive models. Prospective multicenter studies with larger populations are needed to further clarify the role of ALBI in risk stratification and management of HELLP syndrome.

## Ethics Committee Approval

The study was approved by the Etlik Zübeyde Hanım Women's Hospital Ethics Committee (Date: 21.04.2022, Decision No: E-90057706-799-05).

## Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

## Peer-review

Externally peer-reviewed.

## Authorship Contributions

Concept: M.L.D.; Design: S.S., C.I.; Supervision: M.L.D., C.I.; Materials: S.S.; Data collection &/or processing: M.L.D., S.S.; Analysis and/or interpretation: S.S.; Literature search: M.L.D., S.S.; Writing: M.L.D.; Critical review: S.C.

## Conflict of Interest

None declared.

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## Hemoliz, Yüksek Karaciğer Enzimleri ve Düşük Trombosit Sayısı Sendromunu Öngörmeye Albümin-Bilirubin Skorunun Rolü

**Amaç:** Çalışmanın amacı, karaciğer fonksiyon bozukluğunun değerlendirilmesinde kullanılan albumin-bilirubin (ALBI) skorunun, karaciğerin belirgin olarak etkilendiği hemoliz, yüksek karaciğer enzimleri ve düşük trombosit sayısı (HELLP) sendromunun gelişimini öngörmedeki etkinliğini araştırmaktır.

**Gereç ve Yöntem:** Bu retrospektif vaka-kontrol çalışması, 1 Ocak 2018 ile 1 Ocak 2022 tarihleri arasında Ankara'da üçüncü basamak bir merkezde yürütülmüştür. Çalışmaya HELLP sendromu tanısı almış 61 hasta ile birlikte yaş ve gebelik haftaları eşleştirilmiş 122 sağlıklı gebe kadın dahil edilmiştir. Kan örnekleri, HELLP sendromu bulgularının gelişmesinden ortalama 6 hafta önce, gebeliğin 20-28. haftalarında alınmıştır. Tüm katılımcıların demografik, klinik ve biyokimyasal verileri analiz edilmiştir. HELLP sendromu tanısı doğrulanmış hastaların ALBI skorları, öngörü değerini değerlendirmek için regresyon ve alıcı çalışma eğrisi analizleri kullanılarak kontrol grubuyla karşılaştırılmıştır.

**Bulgular:** HELLP grubunda toplam bilirubin düzeyleri anlamlı derecede yüksek iken albumin düzeyleri ise anlamlı derecede düşüktü ( $p < 0.05$ ). Sonuç olarak, ALBI skorları anlamlı derecede yüksekti ( $p = 0.004$ ). Alıcı çalışma eğrisi analizi, ALBI'nin HELLP sendromunu öngörmeye ayırt edici güce sahip olduğunu gösterdi (Eğri altında kalan alan = 0.629;  $p = 0.007$ ). Gerek HELLP grubunda gerekse de katılımcıların tümünün dahil edildiği grupta, ALBI skorunun, kötü kompozit neonatal sonuçların prediksyonunda istatistiksel olarak anlamlı yoktu ( $p > 0.05$ ).

**Sonuç:** Çalışmamızın sonuçlarına göre, karaciğer hastalıkları için özellikle prognoz belirlemede kullanılan ALBI skoru, HELLP sendromunun erken öngörüsünde de kullanılabilir öngörü modelleri arasında yer almaya adaydır. Ancak eşik değerleri ve güvenilirliği doğrulamak için prospektif çok merkezli çalışmalara ihtiyaç vardır.

**Anahtar Sözcükler:** ALBI skoru; gebelik hipertansiyonu; gestasyonel hipertansiyon; HELLP sendromu; karaciğer hastalığı; preeklampsi.

# Clinical and Pathological Characteristics of Gallbladder Polyps: A Retrospective Cohort Study

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**Keywords:** Cholecystectomy; gallbladder neoplasms; polyps; retrospective studies; risk assessment.



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## ABSTRACT

**Objective:** Gallbladder polyps (GPs) are increasingly detected with abdominal ultrasonography; although most are benign, differentiating benign from neoplastic lesions pre-operatively remains challenging. Current guidelines recommend cholecystectomy for polyps  $\geq 10$  mm, yet the true malignancy risk in smaller or symptomatic lesions is still debated.

**Methods:** We performed a single-centre retrospective cohort study of adults ( $\geq 18$  years) who underwent elective cholecystectomy for radiologically confirmed gallbladder polyps. Demographic, clinical, radiological and histopathological data were extracted from electronic records. The primary outcome was histopathological evidence of neoplasia. Categorical variables are presented as n (%), continuous variables as mean  $\pm$  SD or median (IQR).

**Results:** Fifty-seven patients were included (33 women, 24 men; mean age  $45.4 \pm 14.8$  years). Most (50/57, 87.7%) were symptomatic, commonly with right upper-quadrant pain or dyspepsia. Polyps were  $< 10$  mm in 43 patients (75.4%) and  $\geq 10$  mm in 14 (24.6%). Histology revealed cholesterol or other benign polyps in 55 cases (96.5%). Neoplastic change was identified in two patients (3.5%): One benign intraluminal papillary neoplasia and one high-grade intraepithelial neoplasia; both lesions occurred in polyps  $\geq 10$  mm. No neoplasia was found in polyps  $< 10$  mm. Sex, symptom status and polyp multiplicity were not associated with neoplastic transformation.

**Conclusion:** In this cohort, neoplastic transformation was confined to polyps  $\geq 10$  mm, reinforcing the 10-mm threshold for prophylactic cholecystectomy. Polyps  $< 10$  mm—especially in asymptomatic patients—were uniformly benign, supporting conservative ultrasound surveillance. Larger, prospective studies are warranted to refine risk stratification for intermediate-sized lesions.

## INTRODUCTION

Gallbladder polyps (GPs) are mucosal projections into the gallbladder lumen and are frequently detected incidentally during abdominal ultrasonography.<sup>[1]</sup> They are broadly classified as benign or malignant. Benign polyps include cholesterol polyps, inflammatory polyps, and hyperplastic polyps, while adenomatous polyps have malignant potential. Cholesterol polyps, which are caused by the accumulation of cholesterol esters in macrophages, represent the most common type.<sup>[2]</sup> Inflammatory and hyperplastic polyps are less common but are generally considered benign.<sup>[3]</sup> Adenomatous polyps, although less prevalent, are of particular concern due to their potential for malignant transformation.<sup>[4]</sup> Distinguishing between benign and malignant polyps remains a significant challenge in clinical practice, as imaging characteristics alone are often insufficient to determine malignancy.<sup>[5]</sup>

Most gallbladder polyps are asymptomatic and are discovered incidentally during imaging studies performed for unrelated reasons.<sup>[6]</sup> When symptomatic, patients may present with non-specific symptoms such as right upper quadrant pain, dyspepsia, nausea, or biliary colic.<sup>[6]</sup> The clinical significance of gallbladder polyps stems from their potential to undergo neoplastic transformation. Size is considered the most important predictive factor for malignancy, with polyps larger than 10 mm having a higher likelihood of being malignant.<sup>[7]</sup> However, other features such as rapid growth, patient age, sessile morphology, and the presence of gallstones have also been associated with increased malignant potential.<sup>[8]</sup>

Current guidelines recommend cholecystectomy for gallbladder polyps larger than 10 mm or those demonstrating rapid growth, as these characteristics are strongly correlated with an increased risk of malignancy.<sup>[9]</sup> However,

the management of smaller polyps remains controversial. Some studies suggest that polyps smaller than 6 mm rarely harbor malignancy and can be monitored with serial ultrasonography. For polyps between 6 mm and 10 mm, the decision to proceed with cholecystectomy is influenced by additional risk factors such as patient age, polyp morphology, and the presence of gallbladder wall thickening.<sup>[10,11]</sup>

Despite the availability of guidelines, the management of gallbladder polyps remains highly individualized, with variability in clinical practice. The decision to perform cholecystectomy often depends on the surgeon's experience, patient preference, and institutional protocols. Understanding the clinical, radiological, and pathological characteristics of gallbladder polyps and their correlation with malignancy is essential for developing evidence-based management strategies and improving patient outcomes.<sup>[12]</sup>

This study aims to retrospectively evaluate the clinical, radiological, and pathological characteristics of gallbladder polyps in a cohort of patients who underwent cholecystectomy. By analyzing factors associated with malignancy, we aim to provide insights into optimizing the management of gallbladder polyps and improving the accuracy of preoperative risk assessment.<sup>[13]</sup>

## MATERIALS AND METHODS

### Study Design and Setting

This retrospective cohort investigation was carried out at a single tertiary hospital. Patient information covering the interval from January 2022 to December 2024 was abstracted from electronic health records and paper charts. The protocol adhered to the Declaration of Helsinki and received institutional review board approval (No: AEŞH-BADEK-2024-1204, Date, 25/12/2024); informed-consent requirements were waived because the study relied exclusively on previously documented data.

During the study period, a total of 5,354 cholecystectomies were performed, and among them, 57 (0.01%) underwent cholecystectomy for gallbladder polyps. This subgroup constituted the study population.

Patients with asymptomatic or small polyps (<10 mm) who did not meet surgical criteria were followed up with annual abdominal ultrasonography in the outpatient clinic. Given the high patient load, the extensive number of ultrasonographic examinations performed, and the routine practice of managing many gallbladder polyp cases conservatively under sonographic surveillance, it was not feasible to retrospectively ascertain the exact number of patients followed non-operatively.

The study population consisted of 57 patients who underwent cholecystectomy for gallbladder polyps. The inclusion and exclusion criteria were carefully defined to minimize selection bias and ensure the accuracy of data analysis (Fig. 1).

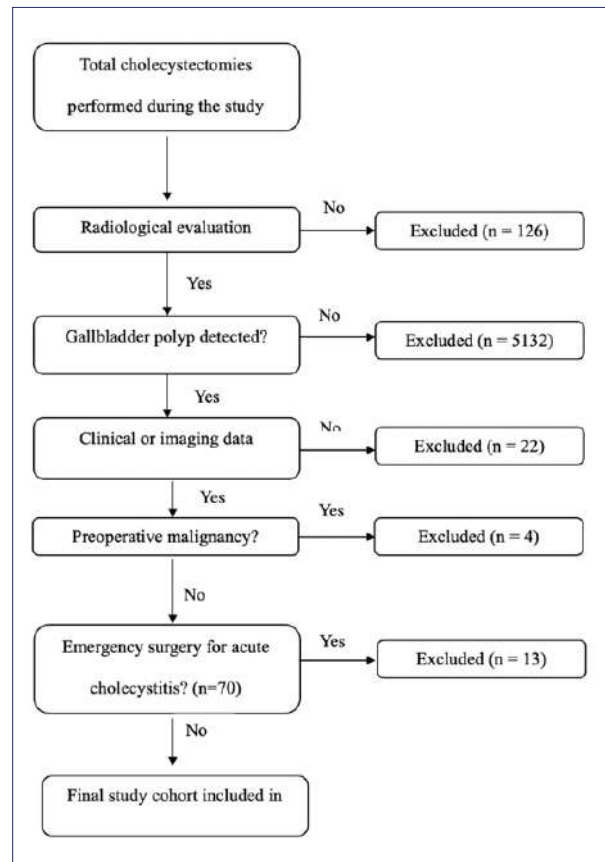


Figure 1. Algorithm of patient inclusion and exclusion.

### Data Collection

Data were extracted from the hospital's electronic medical record system and patient charts. The collected data included detailed demographic, clinical, radiological, surgical, and histopathological variables:

- Demographic data: Age, sex, and comorbidities (e.g., diabetes, hypertension).
- Clinical data: Symptoms at presentation (e.g., pain, dyspepsia, nausea), symptomatic or asymptomatic status, duration of symptoms.
- Radiological data: Polyp size (maximum diameter), number of polyps, morphology (sessile or pedunculated), wall thickening, and the presence of gallstones or sludge.
- Surgical details: Type of surgery (laparoscopic or open), duration of surgery, intraoperative complications, and conversion to open surgery.
- Histopathological findings: Polyp type (cholesterol, adenomatous, inflammatory, hyperplastic), presence of dysplasia, malignancy, and coexisting gallbladder pathology (e.g., cholecystitis, cholesterosis).

The primary outcome measure was the presence of malignancy in the histopathological examination of gallbladder polyps. Secondary outcome measures included the correlation between polyp size and malignancy, association of

demographic and clinical factors with malignancy, and the rate of postoperative complications.

Data were summarised with descriptive statistics. Categorical variables are reported as counts and percentages, whereas continuous variables are expressed as mean  $\pm$  standard deviation for normally distributed data or median (interquartile range) when skewed. All analyses were conducted with SPSS, version 23 (IBM Corp., Armonk, NY, USA).

## RESULTS

In this retrospective observational study, a total of 57 patients who underwent elective cholecystectomy due to gallbladder polyps between January 2022 and December 2024 were included in the final analysis. Of the included cases, 33 patients (57.9%) were female, while 24 patients (42.1%) were male, indicating a modest female predominance. The mean age of the entire study cohort was calculated as 45.4 years, with the youngest patient aged 18 and the oldest aged 77 years. When stratified by sex, female patients had a higher mean age of 50.4 years compared to 38.5 years among their male counterparts, suggesting a possible age-related trend in gallbladder polyp development or presentation.

The overwhelming majority of the cohort (n=50, 87.7%) presented with a variety of gastrointestinal symptoms that prompted further evaluation (Table 1). The most commonly reported symptoms were dyspepsia, right upper quadrant (RUQ) abdominal pain, and intermittent episodes of nausea, which are often non-specific but frequently associated with gallbladder pathology. Conversely, only seven patients (12.3%) were asymptomatic, and their polyps were discovered incidentally during abdominal

imaging performed for unrelated reasons such as general health screening or investigation of other abdominal complaints. Interestingly, all asymptomatic individuals had polyps measuring less than 10 mm in diameter.

In patients with symptomatic polyps <10 mm, additional upper gastrointestinal (GIS) causes of dyspepsia or pain (such as gastritis, reflux disease, or peptic ulcer) were assessed. Gastroscopy was performed in 18 patients (31.6%) and revealed no significant pathology that could account for the symptoms in any case.

Regarding polyp size, 43 patients (75.4%) had polyps smaller than 10 mm, while the remaining 14 patients (24.6%) presented with polyps that were equal to or greater than 10 mm. A size threshold of 10 mm is frequently considered clinically significant due to its established association with increased malignancy risk. Among those with polyps  $\geq$ 10 mm, symptoms such as RUQ pain and dyspeptic complaints were more prevalent, suggesting a potential correlation between polyp size and symptomatic manifestation. In terms of number, most patients (n=48, 84.2%) were found to have a solitary polyp upon pathological evaluation, whereas nine patients (15.8%) had multiple polyps. This finding reinforces the notion that solitary polyps are more common in the general population undergoing cholecystectomy for polyp-related indications.

Histopathological assessment of the resected gallbladders revealed that the vast majority of cases (n=55, 96.5%) were non-neoplastic in nature (Table 2). These lesions included cholesterol polyps, fibrous hyperplasia, and other benign alterations associated with chronic inflammation. Only two patients (3.5%) were found to have neoplastic changes. One of these cases was characterized by benign intraluminal papillary neoplasia, while the other exhibited high-grade intraepithelial neoplasia, a finding suggestive of

**Table 1.** Clinical characteristics and polyp size distribution

Parameter	Total (n=57)	Female (n=33)	Male (n=24)	Notes
Age (years)	45.4 (18–77)	50.4 (18-77)	38.5 (23-64)	Mean age with overall range
Clinical Presentation				
Symptomatic	50 (87.7%)	28	22	Predominantly dyspepsia, RUQ pain, and/or nausea
Asymptomatic	7 (12.3%)	5	2	All with polyps <10 mm
Polyp Size				
<10 mm	43 (75.4%)	22	21	Majority; frequently associated with benign findings
$\geq$ 10 mm	14 (24.6%)	11	3	More often associated with prominent symptoms and neoplastic changes
Polyp Number				
Solitary	48 (84.2%)	27	21	
Multiple	9 (15.8%)	6	3	

Table 1 presents the demographic and clinical characteristics of 57 patients with gallbladder polyps, stratified by sex. The mean age was 45.4 years, with a slightly higher mean age observed in females (50.4 years) compared to males (38.5 years). Most patients (87.7%) were symptomatic, commonly presenting with dyspepsia, right upper quadrant pain, and nausea. Among the polyps, the majority (75.4%) were smaller than 10 mm, with these smaller polyps typically associated with benign findings. In contrast, larger polyps ( $\geq$ 10 mm) were more frequently linked to notable symptoms and potential neoplastic changes. Additionally, most polyps were solitary (84.2%), while 15.8% of patients had multiple polyps.

**Table 2.** Histopathological findings and gender distribution

Histopathological Category	Total (n=57)	Female (n=33)	Male (n=24)	Additional Details
No Neoplasia	55	32	23	In 53 cases, chronic cholecystitis was noted, with additional benign findings (cholesterol polyps, cholelithiasis, etc.)
Chronic cholecystitis	49	22	27	8 patients without chronic cholecystitis
Neoplastic Changes	2 (3.5%)	1	1	One case of benign intraluminal papillary neoplasia and one case of high-grade intraepithelial neoplasia; both in the $\geq 10$ mm group
Other Benign Findings	5	3	2	
Adenomyomatosis	2	2	0	
Inflammatory polyp	1	0	1	
Hyperplastic polyp	2	1	1	

Table 2 summarizes the histopathological findings in 57 patients with gallbladder polyps, categorized by gender. The majority of cases (55/57) showed no neoplastic changes, with 53 of this exhibiting chronic cholecystitis accompanied by benign conditions such as cholesterol polyps or cholelithiasis. Chronic cholecystitis was present in 49 patients, with 8 patients not demonstrating this pathology. Neoplastic changes were identified in two cases (3.5%), consisting of one benign intraluminal papillary neoplasia and one high-grade intraepithelial neoplasia, both associated with polyps  $\geq 10$  mm. Other benign findings included adenomyomatosis (n=2), inflammatory polyps (n=1), and hyperplastic polyps (n=2), with slight gender variations in distribution.

**Table 3.** Comparison of clinical and demographic characteristics by gallbladder polyp size

Variable	Total (n=57)	<10 mm Polyp (n=43)	$\geq 10$ mm Polyp (n=14)
Age, years (mean $\pm$ SD)	45.4 $\pm$ 12.6	44.2 $\pm$ 11.9	48.7 $\pm$ 13.3
Female sex, n (%)	33 (57.9)	24 (55.8)	9 (64.3)
Symptomatic, n (%)	50 (87.7)	36 (83.7)	14 (100)
Common symptoms, n (%)			
Dyspepsia	31 (54.4)	22 (51.2)	9 (64.3)
RUQ pain	29 (50.9)	20 (46.5)	9 (64.3)
Polyp multiplicity, n (%)			
Single polyp	48 (84.2)	36 (83.7)	12 (85.7)
Multiple polyps	9 (15.8)	7 (16.3)	2 (14.3)

Table 3 compares the clinical and demographic characteristics of patients based on polyp size (<10 mm vs.  $\geq 10$  mm). The mean age was higher in patients with larger polyps (48.7 $\pm$ 13.3 years) compared to those with smaller polyps (44.2 $\pm$ 11.9 years). The prevalence of symptomatic cases was notably higher in the  $\geq 10$  mm group (100%) than in the <10 mm group (83.7%). Common symptoms such as dyspepsia and right upper quadrant (RUQ) pain were more frequent in patients with larger polyps. Polyp multiplicity was comparable between the groups, with single polyps being the predominant finding in both size categories.

pre-malignant transformation. Notably, both of these neoplastic lesions occurred in patients with polyps measuring  $\geq 10$  mm, further supporting the clinical importance of polyp size as a predictive factor for malignancy risk.

Chronic cholecystitis was observed in 49 patients, representing 85.9% of the entire cohort. This was often accompanied by cholesterol polyps or associated with cholelithiasis, suggesting a multifactorial inflammatory etiology. In contrast, eight patients did not show any histological evidence of chronic inflammation in their gallbladder specimens. Additional benign findings included adenomyomatosis in two patients, hyperplastic polyps in two patients, and

a single case of inflammatory polyp. These findings highlight the heterogeneity of gallbladder polyp pathology and the importance of thorough histopathological examination following cholecystectomy.

A comparative analysis between male and female patients revealed no statistically significant differences in terms of neoplastic transformation. Among the 33 female patients, one neoplastic lesion was detected, and similarly, one neoplastic lesion was found in the group of 24 male patients. This suggests that gender may not play a significant role in the likelihood of neoplastic progression of gallbladder polyps. Furthermore, both neoplastic cases involved

polyps  $\geq 10$  mm, consistent with previously reported literature indicating that polyp size, rather than gender, is a more critical factor in predicting neoplastic potential. It is also worth noting that polyps  $< 10$  mm were almost universally associated with benign histopathological outcomes across both sexes.

When correlating clinical presentation with histopathological results, a clear pattern emerged. All asymptomatic patients had polyps smaller than 10 mm and exhibited benign histological features, most commonly cholesterol polyps or findings suggestive of incidental cholelithiasis. In contrast, symptomatic individuals, particularly those presenting with larger polyps ( $\geq 10$  mm) were more likely to show pathological evidence of chronic cholecystitis and, in rare cases, neoplasia (Table 3). These findings underscore the diagnostic relevance of combining clinical symptomatology with imaging and size-based assessment to guide treatment decisions and risk stratification. The presence of symptoms in patients with large polyps should prompt clinicians to maintain a heightened index of suspicion for potential histopathological abnormalities.

## DISCUSSION

The most prominent finding of this study is the extremely low rate of neoplastic transformation among patients who underwent cholecystectomy for gallbladder polyps. Only two cases (3.5%) demonstrated neoplastic changes, and both were associated with polyps  $\geq 10$  mm. This clear separation between small and large polyps reinforces the size-dependent risk pattern observed in several international series and supports the risk stratification thresholds adopted in contemporary guidelines. The complete absence of neoplasia among polyps  $< 10$  mm in our cohort further indicates that conservative management is a safe and reasonable strategy for small lesions.

The second notable pattern in our data is the demographic distribution. Our cohort was younger than most Western populations described in recent reports and showed a female predominance. While our sample size limits firm conclusions, this trend suggests that regional or population-specific factors may influence GP epidemiology. The older age of female patients compared with males may also reflect more frequent imaging in women undergoing evaluation for biliary or gastrointestinal symptoms.

Histopathological analysis in our study showed that almost all polyps were benign, most commonly cholesterol polyps. Histopathologically, cholesterol polyps dominated our series, which is consistent with prior reports describing these lesions as comprising 60–90% of all GP.<sup>[14,15]</sup> Moreover, the histopathological spectrum also included inflammatory and hyperplastic polyps, with adenomyomatosis and fibrous hyperplasia occasionally identified. This variety underscores the heterogeneity of gallbladder mucosal lesions and the limitations of preoperative imaging in accurately predicting polyp pathology.<sup>[16]</sup>

The discrepancy between radiological findings and

histopathology once again highlights the limitations of ultrasonography. Although USG is useful in detecting polyps, it is not sufficiently reliable in distinguishing between benign and neoplastic lesions; therefore, size and growth rate should be more decisive in the decision-making process.

A critical clinical implication of our findings is the reaffirmation of the 10 mm size threshold as a significant predictor of neoplastic potential. Both patients with neoplastic lesions in our study had polyps  $\geq 10$  mm, in agreement with prior reports, who reported that malignant or pre-malignant changes are rarely observed in polyps smaller than this size.<sup>[17,18]</sup> Our study also observed that all polyps  $< 10$  mm were histologically benign, further supporting the safety of conservative management for small, asymptomatic polyps.

Our findings mirror the revised algorithm proposed in the 2023 ESGAR/EAES/ESGE guideline (prioritising cholecystectomy for polyps  $\geq 10$  mm or those showing rapid interval growth) and are further supported by the 2024 systematic review by Wang et al.,<sup>[2]</sup> which reached identical conclusions on size- and growth-based risk stratification.<sup>[19,20]</sup>

Interestingly, we observed no statistically significant association between sex and the presence of neoplastic lesions. Although previous studies have noted a slight male predominance in malignancy-associated polyps our findings suggest that gender may not be a reliable standalone risk factor.<sup>[21]</sup> Instead, polyp size, patient age, and symptoms appear to be more relevant in risk stratification. It is worth noting, however, that female patients in our cohort were significantly older than males, which might reflect a greater prevalence of comorbid biliary conditions or incidental detection in older populations undergoing more frequent imaging.

## Strengths and Limitations

The strengths of this study include a focused cohort with histologically confirmed diagnoses and comprehensive data on clinical, radiological, and pathological parameters. However, the study has several limitations. The principal limitations of this study are its small sample size, single-center design, and absence of long-term follow-up data. Additionally, the inability to retrieve complete data on non-operatively managed polyps limits broader epidemiological interpretation.

## CONCLUSION

Our findings reinforce current guidelines that advocate for cholecystectomy in symptomatic patients and those with gallbladder polyps  $\geq 10$  mm due to the increased risk of neoplastic transformation. Polyps  $< 10$  mm, particularly in asymptomatic individuals, were overwhelmingly benign, supporting a conservative follow-up approach in selected patients. While imaging and clinical features can aid in risk stratification, histopathological confirmation remains the gold standard for definitive diagnosis.

Future multicenter prospective studies with larger cohorts and long-term follow-up are needed to refine risk models and optimize management strategies for gallbladder polyps, particularly those in the 6–10 mm range. The development of novel biomarkers or advanced imaging modalities may also help bridge the current gap between radiological suspicion and pathological certainty.

#### Ethics Committee Approval

The study was approved by the Ankara Etlik City Hospital Ethical Committee (Date: 25.12.2024, Decision No: AEŞH-BADEK-2024-1204).

#### Informed Consent

Informed-consent requirements were waived because the study relied exclusively on previously documented data.

#### Peer-review

Externally peer-reviewed.

#### Authorship Contributions

Concept: M.S.S.; Design: S.D.; Supervision: S.B.; Materials: S.D., S.B.; Data collection &/or processing: S.D.; Analysis and/or interpretation: M.S.S., S.D.; Literature search: S.D., S.B.; Writing: M.S.S.; Critical review: S.D., S.B.

#### Conflict of Interest

None declared.

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## Safra Kesesi Poliplerinin Klinik ve Patolojik Özellikleri: Retrospektif Kohort Çalışma

**Amaç:** Safra kesesi polipleri (SKP), abdominal ultrasonografi ile giderek daha sık saptanmaktadır. Çoğu benign olmakla birlikte, preoperatif dönemde benign ve neoplastik lezyonların ayırt edilmesi güçtür. Mevcut kılavuzlar  $\geq 10$  mm poliplerde kolesistektomi önermektedir, ancak daha küçük veya semptomatik poliplerde malignite riski tartışmalıdır.






**Gereç ve Yöntem:** Radyolojik olarak safra kesesi polibi saptanan ve elektif kolesistektomi uygulanan  $\geq 18$  yaş erişkin hastalar retrospektif olarak incelendi. Demografik, klinik, radyolojik ve histopatolojik veriler kaydedildi. Primer sonuç, histopatolojik olarak neoplazi varlığıydı. Kategorik veriler sayı (%) ile, sürekli değişkenler ortalama  $\pm$  SS veya medyan (IQR) ile sunuldu.

**Bulgular:** Toplam 57 hasta (33 kadın, 24 erkek; ort. yaş  $45.4 \pm 14.8$  yıl) çalışmaya dahil edildi. Hastaların çoğu (%87.7) semptomatikti; en sık sağ üst kadranda ağrısı ve dispepsi izlendi. Kırk üç hastada (%75.4) polip  $< 10$  mm, 14 hastada (%24.6)  $\geq 10$  mm idi. Histopatolojide 55 olguda (%96.5) kolesterol veya diğer benign polipler saptandı. İki hastada (%3.5) neoplastik değişiklik görüldü: Biri benign intraluminal papiller neoplazi, diğeri yüksek dereceli intraepitelyal neoplazi; her iki olgu da  $\geq 10$  mm poliplerdeydi.  $< 10$  mm poliplerde neoplazi izlenmedi. Cinsiyet, semptom durumu ve polip çokluğu ile neoplastik dönüşüm arasında ilişki bulunmadı.

**Sonuç:** Bu kohortta neoplastik dönüşüm yalnızca  $\geq 10$  mm poliplerde görüldü ve profilaktik kolesistektomi için 10 mm eşik değerini destekledi.  $< 10$  mm polipler özellikle asemptomatik hastalarda, tamamen benign bulundu ve ultrason ile konservatif izlem güvenilir görüldü. Orta boyutlu lezyonlar için risk sınıflamasını netleştirmek amacıyla daha geniş, prospektif çalışmalara ihtiyaç vardır.

**Anahtar Sözcükler:** Kolesistektomi; polipler; retrospektif çalışmalar; risk değerlendirmesi; safra kesesi neoplazileri.

# NMO Spectrum Disorder or Mass?

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**Keywords:** Demyelination; glial tumor; nmo; spinal mass.



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## ABSTRACT

Longitudinally extensive transverse myelitis (LETM) generally present a destructive clinical syndrome which has come into focus for its association with neuromyelitis optica spectrum disease (NMOSD). In clinical practice, both LETM and NMO have a close relation so they thought to be synonymous with each other. Other causes of LETM are infective, neoplastic and connective tissue disorders. Similar symptoms and even similar CSF abnormalities can cause difficulties in differential diagnosis. In suspicious cases, beside more detailed history, tight observation of clinical progress and follow-up MRI, pathological evaluation can be helpful to certain diagnosis.

## INTRODUCTION

Longitudinally extensive transverse myelitis (LETM) is a typical feature of neuromyelitis optica, but such spinal lesions can also seen in multiple other autoimmune and inflammatory diseases that involve the CNS (such as acute disseminated encephalomyelitis, multiple sclerosis, sarcoidosis or Sjögren syndrome) or in infectious diseases with CNS involvement. Patients with a neoplastic disorder or traumatic spinal cord injury can also present with longitudinal spinal lesions like inflammatory diseases.<sup>[1]</sup>

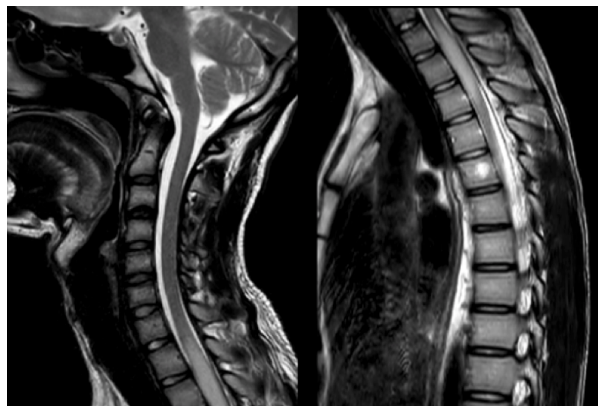
Intramedullary tumours of the spinal cord are quite infrequent. The most common intramedullary tumors are astrocytomas and ependymomas which together account for 90% of them. These lesions can cause important difficulties in the differential diagnosis between inflammatory diseases (such as acute disseminated encephalomyelitis, multiple sclerosis), vascular abnormalities and neoplasms.<sup>[2]</sup>

Intramedullary tumours, particularly ependymomas and astrocytomas often appear hyperintense on T2- weighted

imaging and usually extend across multiple vertebral segments like neuromyelitis optica spectrum diseases.<sup>[3]</sup> Here we report a case which has been treated as NMOSD first but after diagnosed as intramedullary tumor.

## CASE REPORT

18-year-old male patient admitted to our hospital with complaints of weakness and numbness in both legs. It was learned from the patient's history that he was referred to a tertiary care center with bilateral weakness in lower extremities and urinary incontinence complaints which started 40 days ago. In the radiological images performed there, a spinal lesion was detected and pulse steroid was started with a pre-diagnosis of demyelinating disease. After a while, he stated that the weakness partially resolved but started again. He did not state any complaints about vision. Past history included only a vehicle accident one year ago which did not cause any neurological symptom. No alcohol or smoking was reported. There was no feature in his family history.



**Figure 1.** Hyperintense lesion in the t2-weighted imaging along T1-T3



**Figure 2.** Hyperintense lesion in the T2-weighted imaging along C6-T2.

In the neurological examination; muscle strength was detected at upper limb bilateral 5/5, at right lower limb proximal and distal 1/5, at left lower limb proximal 2/5 distal 3/5. Bilateral hypoesthesia was obtained below T12. Bilateral position sense loss, bilateral decreased sense of vibration was detected in lower extremities. Deep tendon reflexes have increased globally. Babinski was extensor on the right and there was no response on the left.

Complete blood count, liver, kidney and thyroid function tests, blood glucose, electrolytes; sodium, potassium, calcium, ionized calcium, phosphorus, magnesium, erythrocyte sedimentation rate and C-reactive protein were normal.

His spinal MR imaging showed a hyperintense lesion was seen extending longitudinally along T1-T3 levels in T2-weighted sections (Fig. 1).

Vitamin B12 level was normal and syphilis serology was negative. The patient underwent lumbar puncture. No cells were seen in the cerebrospinal fluid (CSF). Oligoclonal band in CSF and Serum anti-aquaporin 4 antibody (NMO IgG) were negative. Vasculitis markers, angiotensin converting enzyme level and paraneoplastic markers were negative. There was no finding that could be evaluated in favor of malignancy in thorax CT.

OCT was performed on the patient who did not have symptomatic optic neuritis. On the left superior and inferior; on the right superior and nasal retinal nerve fiber layers (RNFL) thinning was observed.

A diagnosis of seronegative NMO spectrum disorder was considered accompanied by longitudinal transverse myelitis and optic nerve involvement as asymptotically. Along with longitudinal transverse myelitis and optic nerve asymptomatic effect, a diagnosis of NMO spectrum disorder was considered. 0.4 mg / kg / day IVIG treatment was given for 5 days. The patient gained increase his muscle strength with pulse steroid and IVIG treatment was called for a control examination 15 days later.

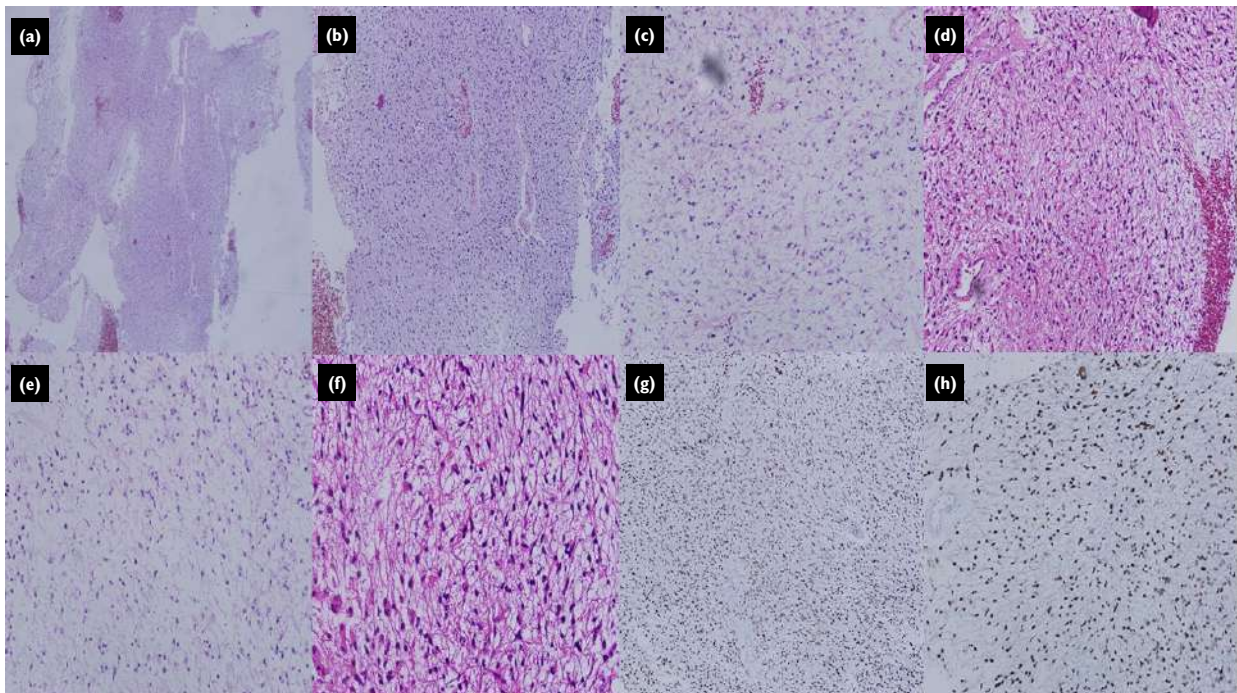
Progression was observed in the control visit. Follow up spinal MRI was taken and expansive view at the thoracic level was shown growth towards the cervix. (Fig. 2) Plasmapheresis was added to treatment scheme but patient had no clinical benefit. Biopsy decision was given and Diffuse midline glial tumor grade 4 was shown (Fig. 3). Tumor was resected by surgeons and radiotherapy was applied to patient.

## DISCUSSION

Current diagnostic criteria of NMO spectrum diseases were published by the International Panel for NMO diagnosis in 2015. The criteria classify the diagnosis by those with AQP4-IgG and those without AQP4-IgG (including those whom AQP4-IgG negative or not tested). The main clinic features are determined as the three cardinal manifestations of optic neuritis, myelitis, and an area postrema syndrome, in addition to less common manifestations of other brainstem attacks, diencephalic episodes, and cerebral episodes. AQP4-IgG positivity and one main feature are sufficient for diagnosis, whereas the criteria for patients who are AQP4-IgG seronegative are more stringent, requiring additional characteristic radiologic features be present to help avoid misdiagnosis.<sup>[4]</sup>

Almost 20% to 25% of patients with NMO spectrum disorder are AQP4-IgG seronegative. The treatment approach is similar in AQP4-IgG-seronegative NMO spectrum disorder and AQP4-IgG-seropositive NMO spectrum disorder; Assay techniques have improved over time, cell-based assays are now recommended and they yield a sensitivity of 75% to 80% and specificity of greater than 99%.<sup>[5]</sup>

Clinical symptoms of intramedullary tumors are nonspecific, including local or less frequently irradiating pain. Motor weakness, gait problems and bowel and bladder dysfunction are another common symptoms of intramedullary tumors.<sup>[6]</sup> Demyelinating disease, MS or ADEM also present with the same symptoms.



**Figure 3.** (a,b,c,d,e,f) Hematoxylin and eosin stain showing neoplastic cells, and (g,h) H3 K27M immunostain showing positive neoplastic nuclei.

In a study conducted by Brinar and friends<sup>[2]</sup> with five cases with spinal lesions presenting with weakness and paresthesia, open biopsy was considered in all patients. It was performed in two patients. Inflammation related tissue has been reported in both.

In the case reported by Habek and friends,<sup>[7]</sup> the patient was admitted with the acute myelopathy clinic, and pulse steroid therapy was started considering the demyelinating disease. Although the treatment, progression was continued as clinical and radiologically. Biopsy was performed and interpreted as an intramedullary tumor. Intense inflammation was seen in pathology. Additionally performed CSF analysis, which revealed positive oligoclonal IgG bands. Serum NMO-IgG antibody was positive. The patient was diagnosed with spatially limited NMO spectrum disorder, treated with plasma exchange, high-dose corticosteroids, and cyclophosphamide, and recovered well.

In the case reported by Jakob and friends<sup>[8]</sup> Inflammatory LETM has been considered due to its clinical features, oligoclonal band positivity and positive response to corticosteroid treatment. Biopsy performed and spinal tumor was diagnosed.

In our case, seronegative NMO Spectrum disease was considered in the patient who had transverse myelitis attacks and had asymptomatic optic neuritis findings. Despite applying pulse steroid, ivig and plasmapheresis treatments, clinical and radiological progression continued. Biopsy was performed considering intramedullary mass in differential diagnosis, midline diffuse glial tumor stage 4 was detected.

## CONCLUSION

Although longitudinal extensively spinal cord lesions are most frequently caused by inflammatory lesions (especially NMO), non-inflammatory causes should also be considered. Clinic of myelopathy related with spinal masses deteriorates in an acute-subacute course but it should be remembered that acute-subacute onset can also be observed in advanced masses with rapid progression.

Clinical features, neurological examination, laboratory tests and MRI findings should be evaluated together. Suspicious cases should be followed up closely. Clinical and radiologic progression despite the treatment should alert clinician.

### Informed Consent

Retrospective study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: N.Y.A, A.K.K.; Design: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Supervision: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Fundings: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Materials: D.I.; Data: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Analysis: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Literature search: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Writing: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.; Critical revision: N.Y.A, A.K.K., D.Y., T.H., B.Ö.B.

### Conflict of Interest

None declared.

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### NMO mu? Kitle mi?

Longitudinal yayılan transverse miyelit, genellikle nöromyelitis optika spektrum hastalıkları ile ilişkili ağır bir kinik sendrom olarak ortaya çıkar. Ancak etiolojide otoimmün nedenler yanında enfektif, neoplastik ve bağ doku hastalıkları ile ilişkili süreçler bulunabilir. Benzer semptomlar ve BOS bulguları ayırıcı tanıda zorluğa sebep olabilir. Şüphe durumunda; ayrıntılı öykü, yakın klinik ve görüntüleme yanında patolojik değerlendirme doğru tanıya ulaşmada yönlendirici olabilir.

**Anahtar Sözcükler:** Demiyelinizan; glial tumor; nmo, spinal kitle.

# Nursing Care of the Individual with Flame Burn According to the Nursing Model Based on Daily Living Activities of Roper, Logan and Tierney

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**Keywords:** Burn; care; model; nursing.



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## ABSTRACT

Burn victims consist a wide range of industrial accidents. The trauma arose from industrial burn accidents bring forth disability or even death. Not only the victim but also the family suffer from this situation. It is thought that the Nursing Model, which consists of five items (life time, daily life activities, factors those affecting daily life activities, independency-dependency system, individuality in life), collects data about the individual patient and apply it in a systematic direction with a holistic approach. The aim of this study is how to take care of the patients, those suffered from burn injury as a result of an industrial accident in accordance to the Nursing Model based on the daily life activities of Roper-Logan and Tierney.

## INTRODUCTION

Burn is a comprehensive trauma that affects the whole organism.<sup>[1]</sup> According to the American Burn Association data, 450,000 people were injured due to burns and 3400 individuals lost their lives in 2012. These deaths; 2850 of them were due to flame burn, 150 of them were inhalation damage, 400 of them were due to electricity, scalding and hot body contact.<sup>[2]</sup> Despite the great advances in technology and medicine today, burns are still life threatening problems.<sup>[3,4]</sup> According to the Social Security Administration data in Turkey, 359 653 insured individuals who have work accidents in 2017. 1633 of them died.<sup>[5]</sup> Burn takes

a large place among the causes of work accidents. Burn trauma caused by work accidents can result in death or disability, negatively affecting the lifestyle of the individual and his family.

Various models have been developed by theorists to ensure systematic and comprehensive collection of data from a healthy/ill individual/family. One of these models is the Roper, Logan and Tierney's Nursing Model based on daily life activities, consisting of five items (life span, activities of living, factors influencing activities of living, independence-dependency continuum, individuality). The model is thought to provide holistic care by collecting data about the individual in a systematic direction.<sup>[6]</sup> The aim

of this study is to discuss the care process of the patient who suffered a burn injury as a result of a work accident in according to Roper, Logan and Tierney' Nursing Model based on the daily living activities.

## CASE REPORT

A 47 year old male patient was brought to our center by the 112 emergency ambulance. He approached the tube leak with lighter fire at work and as a result of the explosion of the tube, a third degree burn occurred in 47.3% of his body (Head 5%, neck 1%, Front body 3%, Back 4%, Right Gluteal region 1%, Right upper arm 3%, Right forearm 2%, Right hand 2.5%, Left upper arm 1% Left Forearm 2%, Left hand 2%, Right leg 10%, Right foot 1%, Left leg 8%, Left foot 1%).

After his first treatments, he was hospitalized in the Burn Intensive Care Unit. In the first evaluation, the general condition of the individual was confused, the Glaskow Coma Scale was evaluated as 14/15, respiratory distress was present, dehydrated appearance and peripheral pulses were diagnosed filiform. The individual was intubated and connected to the respiratory equipment, laboratory tests were performed and fluid treatment was started by inserting a central venous catheter. Afterwards, an eschatomy was opened and wound care was performed. After the consultation of the burn treatment team and the necessary units (orthopedics, plastic surgery, neurology, cardiology, eye, nutrition, physical therapy, psychiatry, anesthesia), nutrition and movement supports were decided.

According to the individual's life span, he is in adulthood. While he was fully independent in many ways during his adulthood, he became dependent. When we evaluate the daily life activities of the individual, first of all, he was considered to be dependent on respiratory activity by having respiratory distress and connecting to the respiratory device. Due to the presence of impaired consciousness, not being able to move on his own, and having pain, he was considered to be dependent on the activity of providing a safe environment. It is also semi dependent in communication activity with its intubation and the application of sedative drugs. It was evaluated as a semi dependent in nutritional activity and elimination activity due to the lack of oral nutrition, increased body calorie needs, and unconscious weight loss. It was evaluated as a semi dependent in movement activity with its inability to move on its own, having pain, causing dressing limitation. He is also semi dependent on sleep activity due to missing his family during hospitalization, presence in a hospital environment where he is foreign, pain, infection, daily dressing changes. It was determined that the individual had problems and became semi dependent in the activities of personal cleaning and dressing, control of body temperature, working and entertainment, and expressing sexuality.<sup>[6-9]</sup> The individual was diagnosed with 40 nursing diagnoses according to daily living activities;

- Maintaining a safe environment; risk of infection, acute

pain, acute confusion, risk of trauma, risk of fluctuation in blood sugar level, risk of falling, shock risk

- Communicating; Impaired verbal communication, anxiety, spiritual distress, impaired body image, social isolation
- Breathing; impaired breathing pattern, impaired gas exchange, risk of ineffective airway cleaning, aspiration, risk of ineffective peripheral tissue perfusion
- Eating and drinking; fluid volume deficiency, unbalanced nutrition: Less than body requirement, risk of fluid volume imbalance, risk of electrolyte imbalance, risk of ineffective gastrointestinal perfusion, nausea
- Eliminating; risk of constipation
- Personal cleansing and dressing; lack of self-care in bathing, lack of self care in toilet activities, lack of self care in dressing, lack of self care in nutrition, lack of information, risk of pressure injury, risk of impaired oral mucous membrane, impaired skin integrity
- Controlling body temperature; risk of perioperative hypothermia, hyperthermia
- Mobilizing; impaired in-bed mobility, impaired physical mobility, Activity intolerance
- Working and playing; interrupted family processes, impaired comfort, risk of difficulty in caregiver role
- Sleeping; impaired sleep pattern

Nursing interventions were planned and implemented according to the principle of individuality in life (Table 1).

## DISCUSSION

He was hospitalized in our intensive care unit for 49 days, in the service for 21 days, 70 days in total. Burn wounds were infected and they were cared for. During hospitalization, a total of 30 debridement dressings, 3 autografts and 1 allograft surgery were performed.

Tissue integrity was provided before the discharge of the individual, and their training on nutrition, movement, wound care, and the use of pressure clothing were given. In daily living activities that the individual is dependent to, the levels of dependent were reduced and he was discharged in a position to perform his self care.

As a result, the individualized nursing care planned in according to the NANDA-I, NIC and NOC taxonomic structures and the Roper, Logan, Tierney's Daily Living Activities, in accordance with the stages of the nursing process, increased the level of independence in all living activities by providing holistic care.

### Informed Consent

Retrospective study.

### Peer-review

Externally peer-reviewed.

### Authorship Contributions

Concept: A.K., D.O., G.F., M.Ş.; Design: A.K., D.O., G.F.,

**Table 1.** Part of nursing care process

Nursing Assessment and Nursing Diagnosis	Planning		Implementantation	Evaluation
	Patient Outcomes	Nursing Intrventions		
<p><b>Impaired Spontaneous Ventilation,</b> Related to intense secretion and laryngeal edema as evidenced by decrease in lung sounds, pulse 128 / min., breathing is irregular, superficial and difficult, accompanying respiratory and intercostal/supraclavicular muscles.</p>	<p>There will be effective and equal signs of ventilation in the patient's lung sounds at the end of the day. The patient will have an unassisted breathing pattern until discharge.</p>	<p>The speed, rhythm, depth and breathing effort of breathing are monitored. The expansion of the lungs evenly is checked. The diaphragm is followed in terms of paradoxical movement. Effective coughing of the patient is followed. Aspiration requirement of the airways is defined. Oxygen saturation and blood gas values are monitored. When tolerated, it is gradually separated from mechanical ventilation and oxygen support.</p>	<p>Interventions were implemented</p>	<p>The patient was followed up for a total of 97 hours of mechanical ventilation during his hospitalization. He was taken to the appropriate physical therapy program 1 day after his hospitalization, and 7 days later, he was mobilized 2 times a day for 2 hours. He did not need oxygen supplements 25 days before his discharge.</p>
<p><b>Impaired skin integrity</b> Related to 3rd degree burn injury as a result of flame, as evidenced by Wound in 47.3% of his body.</p>	<p>Tissue integrity will be maintained until the patient is discharged</p>	<p>The integrity of the texture is evaluated. Appropriate asepsis is provided during dressing and other procedures The granulated wound bed is protected from trauma. Extremities are observed in terms of color, temperature, swelling, pulses, tissue, edema and ulceration. Skin and mucous membranes are observed for redness, excessive temperature and discharge. Pressure and friction sources are monitored. The next day of his admission, he is taken to the appropriate exercise program by the FTR. Changes in skin or mucous membranes are recorded. The family member / caregiver is properly trained about the symptoms of skin damage.</p>	<p>Interventions were implemented.</p>	<p>Upon arrival in our unit, Braden Scale score was evaluated as 9 points (high risk). After 20 days, it was evaluated as 18 points (no risk). Pressure injury did not develop. At the end of appropriate dressing and care, 100% tissue integrity was achieved 20 days after the 4th grafting surgery.</p>
<p><b>Liquid Volume Deficiency</b> Related to loss of the volume from the burn wound by evaporation, increased capillary permeability, inability to take oral as evidenced by increased urine concentration, CVP 1mm/Hg2O measurement, Besides measuring 5005cc urine daily and 2020cc urine it extracts; invisible losses, open wounds, stress and fluid losses are high. Occasional hourly urine output to be 20 cc.</p>	<p>The fluid that the patient receives and removes until the end of the day will be balanced and the necessary fluid intake will be provided.</p>	<p>Blood pressure, heart rate, and breathing status are monitored. Fluid requirement in the first 24 hours is calculated according to Parkland Formula (15000cc). Fullness in the neck veins, rustling in the lungs, peripheral edema and increased weight are observed. Daily fluid intake and close are monitored. Weight tracking is done. Blood and electrolyte values are monitored. Mucous membrane, skin turgor and thirst are observed. Fluid intake is changed appropriately when necessary.</p>	<p>Interventions were implemented</p>	<p>Urine density was measured as 1020. CVP value reached 6 mm / H<sub>2</sub>O. Balance was achieved between what he took and removed. When he was not taking orally, IV took his fluids from 200 cc / h (RL from 120 cc / h, TPN from 80 cc / h).</p>

M.Ş.; Supervision: A.K., D.O., G.F., M.Ş.; Fundings: A.K., D.O., G.F., M.Ş., U.Y., H.A., T.G.; Materials: A.K., D.O., G.F., M.Ş., U.Y., H.A., T.G.; Data: UY., T.G., H.A.; Analysis: A.K., D.O., G.F., M.Ş.; Literature search: A.K.; Writing: A.K.; Critical revision: A.K., D.O., G.F., M.Ş., U.Y., H.A., T.G.

#### Conflict of Interest

None declared.

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### Roper, Logan, Tierney'in Günlük Yaşam Aktivitelerine Dayalı Hemşirelik Modeli Doğrultusunda Alev Yanığı Olan Bireyin Bakımı

Yanma iş kazalarının nedenleri arasında geniş bir yer tutmaktadır. İş kazaları sonucu ortaya çıkan yanık travması ölüm ya da sakatlıkla sonuçlanarak bireyin ve ailesinin yaşam biçimini olumsuz yönde etkileyebilmektedir. Beş öğeden oluşan (Yaşam süresi, günlük yaşam aktiviteleri, günlük yaşam aktivitelerini etkileyen faktörler, bağımsızlık-bağımlılık dizgesi, yaşamda bireysellik) Roper, Logan ve Tierney'in günlük yaşam aktivitelerine dayalı Hemşirelik Modelinin hasta birey hakkında sistematik doğrultuda veri toplayarak bütüncül bakım verilmesini sağladığı düşünülmektedir. Bu çalışmanın amacı, iş kazası sonucu yanık yaralanması oluşan hastanın Roper, Logan ve Tierney'in günlük yaşam aktivitelerine dayalı Hemşirelik Modeli doğrultusunda bakım sürecini ele almaktır.

**Anahtar Sözcükler:** Hemşirelik bakımı; model; yanık.

# Spina Bifida: An Overview

koza duman

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**Keywords:** Alpha fetoprotein; folic acid; meningocele; mobilization; spina bifida.



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## ABSTRACT

Spina bifida (SB) is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. The prevalence of spina bifida is 1-10 per 1000 births. Diagnosis of SB is usually made prenatally by measurement of alpha fetal protein in the maternal serum at 16 weeks of gestation or by ultrasound of the fetus at 18-20 weeks of gestation. Depending on the lesion, interruption of the spinal cord at the site of the defect causes paralysis of the legs, incontinence of urine and feces, anesthesia of the skin, and deformation of the hips, knees, and feet. Clinical presentation depends both on the level and type of the spinal lesion at the vertebral column. Early surgical repair of the spinal lesion is essential in preventing further deficits and neurological damage. Conventional approach dictates the surgical repair in 48 hours of birth. With the application of this principle, the rate of protection of the infant's spinal cord and nerve roots has increased. Prenatal surgery which is a relatively new approach is proven to be more effective than postnatal surgery in lowering the occurrence of future complications. A child with the SB diagnosis is a life-long rehabilitation patient. Detailed clinical examination and setting age-appropriate goals is the first step for achieving the best possible outcome.

## INTRODUCTION

Spina bifida (SB) is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization. It is a general term which encompasses different types of myelodysplasia which ranges from mild types, such as spina bifida occulta, to severe and clinically significant types as spina bifida aperta.<sup>[1]</sup>

### Clinical And Research Consequences

#### Types of SB

**Spina Bifida Aperta:** When a meningocele and a meningocele (MMC) are diagnosed, both are defined as spina bifida aperta. Myelomeningocele is the most common and most severe type with nerve roots and cord structures herniated in the sac. This lesion usually has congenital paralysis. The spinal cord is open dorsally, forming a placode on the back of the fetus or new-born baby with or without a meningeal sac. If a meningeal sac is present, the lesion is then called as spina bifida cystica.<sup>[2]</sup>

**Spina Bifida Occulta:** In spina bifida occulta, there is no

visible sac. Discoloration, nevus and hair growth in the midline are the only signs that can be observed. It is mostly asymptomatic at birth and carries the risk of developing neurological deficit over time, the main reason for this risk is tethering of the cord. Lesions like lipomeningocele, lipomyelomeningocele, dermoid cyst and dermoid sinus lead to spina bifida occulta.<sup>[3]</sup>

The prevalence of spina bifida is 1-10 per 1000 births.<sup>[4-6]</sup> MMC is the most common form of spina bifida aperta. The estimated incidence of the diagnosis is 1.8 per 10,000 live births in the United States according to the Centers for Disease Control and Prevention (CDC). The figure appears to be higher in Caucasians and Hispanics than in African Americans and Asians. It is critical to keep in mind that 90-95% of affected infants are born without a family history.<sup>[7]</sup>

#### Risk Factors

The etiology of myelomeningocele is often does not depend on a single factor. Environmental, maternal, genetic factors combined lead to the diagnosis. Pesticides, teratogenic factors, radiation exposure, pollution of different

types, organic solvents may be included in environmental factors. Maternal risk factors may vary. Diminished folate level is undoubtedly the best-known risk factor and maternal obesity is particularly notable. In addition, diabetes, hyperthermia, anxiety, caffeine/alcohol consumption, smoking and use of anticonvulsants are also considered as maternal risk factors.<sup>[8-12]</sup> Although there is some genetic predisposition is noted, most of the cases of myelomeningocele are sporadic. However, it is notable that chromosomal anomalies of trisomy 18 or 13 and an affected twin or first-degree relative might increase the risk ratio. Although spina bifida appears to have a familial pattern, it has been previously noted that reported familial relapse patterns cannot be attributed to the effects of a single genetic locus. Despite the decades long endeavor to unravel the affect of genetic factors on the NTD etiology, yet no conclusive evidence is defined.<sup>[13]</sup>

### Diagnosis

Prenatal scanning is the first step. Alpha fetal protein measurement in the maternal serum at 16 weeks of gestation or by screening of the fetus by ultrasound at 18-20 weeks of gestation are the two highly accurate methods (85-90%) used in diagnosis. Positive findings from either of these two screenings should be followed by amniocentesis or detailed sonography, or both.<sup>[14]</sup>

The detection rate of spina bifida aperta using ultrasound goes as high as 100%. Detection of the indirect cranial signs as the “lemon” and the “banana” sign leads the way. The shape of the skull is described by the “lemon” sign whereas the “banana” sign refers to the cerebellum. The sign is based on the downward traction of the cerebellum, most likely caused by the spinal fluid leakage from the defect site.<sup>[15]</sup>

When spina bifida diagnosis is confirmed, ultrasound is used to assess spontaneous leg and foot motion, leg and spine deformities, the presence of a Chiari II malformation and other physical defects.<sup>[16]</sup> Prenatal Magnetic Resonance Imaging (MRI), with ultrafast T2-weighted sequences, can also be used to characterize the Chiari II and other malformations. Such prenatal imaging studies might help to predict neurological deficit and ambulatory potential.<sup>[17,18]</sup>

The prenatal diagnosis of SB is crucial for families who do not plan to terminate the pregnancy, in order to make a perinatal care plan.

### Management

Management of SB is a lifelong concept. Management of myelomeningocele begins with surgical repair. Early surgical repair of the defect site is essential in preventing further deficits and preserving the remaining function. Conventional early approach dictates the surgical repair in 48 hours of birth. Earlier the closure of the neural tube defect, better is the outcomes. Earlier closure results in increased protection of the infant’s spinal cord and nerve roots.<sup>[4]</sup> Prenatal surgery which recommends even earlier intervention compared to “conventional early approach”

is a relatively newer technique proven to be more effective than “conventional early approach” considering future complications and outcome.<sup>[19-21]</sup> Compared with post-natal repair results, in utero treated infants have a lower incidence of moderate to severe hindbrain herniation and hydrocephalus which requires shunting.<sup>[22]</sup>

### Clinical Course

Spinal cord disruption at the site of the defect causes paralysis in the lower extremities, urine and bowel incontinence, skin anesthesia, and musculoskeletal deformation of the hips, knees, and feet.

Clinical presentation depends both on the level and type of the spinal lesion. Type of the lesion occurs in three forms. Complete lesions, incomplete lesions and skip lesions. Complete lesions present with flaccid paralysis, sensorial and reflex loss below the level. In incomplete lesions, voluntary movement or sensation may be preserved to a degree. Skip lesions appear in an interesting feature, while the caudal segments have function, there may be non-functioning segments in between.<sup>[3]</sup>

Neurological impairment severity mainly depends on the affected level. The higher the lesion is located, more severe deficits appear which creates more drastic musculoskeletal symptomatology.<sup>[23,24]</sup> For instance, quadriplegia often caused by cervical lesions. Whereas paraplegia is mostly associated with thoracic and lumbosacral lesions are mostly associated with paraplegia.<sup>[25]</sup> While cervical defect rate is rare, the most common defect location is the lumbosacral region.<sup>[26]</sup>

Muscle imbalance can lead to a wide range of orthopaedic problems at lower extremities such as talipes equinovarus (clubfoot), rocker bottom foot, cavovarus foot and calcaneus foot (result of active dorsiflexion versus paralyzed plantar flexion), valgus deformity of the ankle, tibial torsion, flexion contracture of knees, femoral torsion, hip dysplasia and dislocation (%50), and vertebral deformities such as scoliosis.<sup>[27]</sup>

Orthotic devices are used to maintain appropriate alignment at the hip, knee, ankle and compensate for strength absence required for ambulation. While orthotic devices vary; Parapodium (supports mid-thoracic region to the floor), swivel walker (converts trunk rotation to forward motion) and reciprocal walking orthosis (works on the principle of counteracting hip flexion with hip extension) draw the attention when children with SB require therapeutic ambulation.<sup>[26]</sup>

The motor level is a useful tool to predict mobility expectations and in family education (Table 1).

Decrease in sensation, both superficial and deep, below the defect level is an essential clinical feature to remember. Pressure sores are the most common outcomes caused by superficial loss of sensation. Up to adulthood, 90% of children have a history of one or more pressure ulcers.<sup>[28]</sup> Burns also are not rare. It is important to keep in mind that insensate skin heals slower. In extreme cases, hospi-

**Table 1.** Functional mobility and equipment needs, based on level of impairment. (L4) (AFO: Ankle-foot orthosis, HKAFO: Hip-knee-ankle-foot orthosis, RGO: Reciprocal gait orthosis)

Motor Function	Level of Muscle Involvement	Expected Potential for Ambulation	Recommended Orthoses for Functional or Therapeutic Ambulation	Durable Medical Equipment
T12	Abdominal paraspinal	Non-functional ambulation; therapeutic only	RGO	Stander (at young age) Manual wheelchair
L1	Hip flexors	Household and therapeutic	Long leg: RGO, HKAFO	Manual wheelchair, stander
L2-3	Hip adductors	Household and therapeutic	Long leg: RGO, HKAFO	Manual wheelchair, forearm crutches
L4	Knee extensors	Household and ± community	Short leg: AFO	Manual wheelchair, forearm crutches
L5-S1	Ankle dorsiflexors	Community ambulation	Short leg: AFO	±Forearm crutches, cane
S2	Ankle plantar flexors	Community ambulation	Foot orthoses	None

talizations and surgical interventions may be required.<sup>[29]</sup> Proprioception loss is a serious factor that exacerbates balance and movement deficits. The child's need for visual and auditory vestibular input to maintain balance and the risk of falling increases. It should be kept in mind that like skip motor lesions, skip sensory lesions may also be present and detailed sensory examination is crucial.

Postural defects are not rare. Kyphosis, scoliosis, increased lordosis, anterior pelvic tilt, rotational deformities of the hip and tibia, hip and knee flexion, and foot pronation are frequently encountered in clinical practice. Spinal deformities are more common in high-level lesions and tend to increase with puberty.<sup>[30-32]</sup>

Approximately 25% of SB cases are born with hydrocephalus. After the surgical closure of the lesion, an additional 60% of cases are added to the numbers.<sup>[7,33]</sup> To maintain intracranial pressure in the normal range is vital. Therefore approximately three quarters (70–85%) of children with hydrocephalus due to spina bifida require ventricular shunting.<sup>[7]</sup> If hydrocephalus is left untreated, cerebral cortex is lost as a result of ventricular overgrowth. This process results in both cognitive and motor function loss. However, it should be kept in mind that shunt itself may lead to complications due to dysfunction and infection. It has been observed that shunt dysfunction or cerebral infection can cause epileptic seizures in 30% of cases. Delay in recognition and intervention may result in loss of function or even death.<sup>[3]</sup>

The intellectual levels of the low-level spina bifida cases were higher than the thoracic level cases. Early closure of the lesion, good meningitis prophylaxis and regular follow-up of the shunt affect cognitive functions positively.<sup>[34]</sup>

It is important to monitorize the kidney functions in children with a diagnosis of SB. Kidneys of most of these children function normally at birth. However, sacral nerves (S2–S4), controlling the bladder are almost always dysfunctional since they are mostly located below the defect level. This etiology results in neurogenic bladder symptomatology. A neurogenic bladder which does not empty properly is a cause of urine residue. Residue urine is a facilitator for recurrent urinary tract infections. Its consequences may

be vesicoureteral reflux, hydronephrosis and subsequent kidney damage respectively. Encouraging the use of clean intermittent catheterization and prescribing anticholinergic medication in required cases to decrease bladder spasms play a key role in proper management.<sup>[35,36]</sup>

Similar to the innervation of bladder, the rectal sphincter is also innervated by the sacral nerves (S2). Therefore, neurogenic bowel is a common feature approximately affecting 90% of children.<sup>[4]</sup> Neurogenic bowel symptoms can be seen in a wide range from constipation due to decreased motility to fecal incontinence due to sensitivity loss and lack of voluntary control.<sup>[37]</sup> Bowel management goal is to prevent constipation and/or incontinence and end up with a regularly formed stool. In order to achieve the goals; sticking to a daily commode plan, encouraging fiber rich diet, provide guidance for staying away from carbonated, caffeinated fluids and maintaining proper medical support plays an important role.

Obesity is an insidious problem that is not uncommon. It occurs as a result of the sedentary life of the child and the decrease in the muscle mass of the lower extremities.<sup>[38]</sup> The basal metabolism of these children due to the lack of muscle mass in the legs is slower. Children who have difficulty integrating into social life due to symptoms such as mobility difficulties and incontinence are more attracted to domestic sedentary activities. Obesity should be followed with the utmost care, as it has adverse effects on ambulation potential.

It is crucial to be alert about tethered cord (tension on the spinal cord) which may lead to progressive neurological disorder. Tethered cord is usually an asymptomatic phenomenon. However, 25% of children may present some symptoms. Back pain in mechanical nature (worsened by activity and relieved with rest), pain in the leg, hypertonia, spasms, decreased sensation, muscle weakness in innervated parts of the legs, hyperreflexia including clonus, gait deterioration, aggravated constipation, increasing scoliosis, and decrease in urodynamic functions require medical examination. If symptoms above are positive and progressing; neurosurgery consultation is indicated.<sup>[4]</sup>

**Table 2.** Goals of mobility according to Mobility Guideline by SB Association. (40)

Primary	<ul style="list-style-type: none"> <li>• Develop expectations for mobility based on age and neurologic level.</li> <li>• Understand and utilize appropriate mobility devices and therapy interventions to optimize mobility across the age spectrum.</li> </ul>
Secondary	<ul style="list-style-type: none"> <li>• Reduce the threats and effects of pain, aging, neurologic deterioration, and obesity on mobility.</li> <li>• Reduce risk of pressure injuries.</li> <li>• Maximize safe functional mobility and acquisition of developmental milestones for social and environmental exploration.</li> <li>• Maximize safe and functional mobility for Activities of Daily Living (ADL), as well as, social, recreational, and pre-vocational/vocational goals.</li> </ul>
Tertiary	<ul style="list-style-type: none"> <li>• Understand how primary and secondary outcomes affect quality of life.</li> </ul>

## Rehabilitation

In every human being physiological and psychological factors complement each other. It is important to keep in mind that children with SB is not an exception to this rule and rehabilitation programs should be planned accordingly. Detailed clinical examination and setting age-appropriate goals is the first step on this hard-packed road for achieving the best possible outcome. Promoting overall wellness, encouraging self-care management and independence by supporting mobility delineates the rehabilitation motto.<sup>[39]</sup>

Mobility impacts not only physical parameters like preserving range of motion, muscle mass, bone density, cardiovascular fitness and endurance but psychological parameters like stress management. It also has beneficial side effects like encouraging community engagement and nurturing cognitive abilities.<sup>[40]</sup> Therefore, each child should be heartened to move in the best possible way even he/she is facing significant limitations, even in the risk of losing that mobility as an adolescent or adult.<sup>[27]</sup>

Since mobility is the key aspect in rehabilitation planning, SB Association (the national organization in the United States representing individuals of all ages) declared a guideline in year 2018.<sup>[40]</sup> According to the guideline the goals of mobility is set in three consecutive and complementary stations (Table 2).

## CONCLUSION

Spina bifida is a congenital neurological defect that may require lifelong follow-up and management of comorbidities that can affect multiple organ systems. Given the complexity of diagnosis, an orchestrated management is crucial.

Regardless of the lesion level, independence in mobility is pivotal and should be encouraged in every possible way.

### Informed Consent

Not applicable. This study did not involve human participants or patient data.

### Peer-review

Externally peer-reviewed.

## Conflict of Interest

There is no conflict of interest to declare.

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## Spina Bifida: Genel Bakış

Spina bifida (SB), fertilizasyon sonrası dördüncü haftada embriyonik nöral tüpün kapanmasındaki defekt sonucu oluşan bir konjenital malformasyondur. Spina bifida prevalansı 1000 doğumda 1-10 olarak verilmiştir. Tanı 16. gebelik haftasında anne serumunda alfa fetal protein ölçümü veya 18-20. gebelik haftasında fetüsün ultrasonografisi ile doğum öncesi konulur. Oluşan defekt nedeniyle alt ekstremitelerde paraliz, idrar, gaita inkontinansı, duyuşal kusur, alt ekstremitelerde deformasyonlar ile prezente olan klinik tablo oluşur. Klinik tablo spinal lezyonun seviyesi ve tipine göre şekillenir. Erken cerrahi onarım, defisit kontrolü ve nörolojik hasarın progresyonunun önlenmesinde esastır. Konvansiyonel yaklaşım ile, doğumdan en geç 48 saat sonra yapılan defekt tamirinin progresyonu önlemede etkili olduğu bilinmektedir. Bu prensibin uygulanması ile bebeğin omurilik ve sinir köklerinin korunma oranı artmıştır. Daha erken girişim imkanı sağlayan prenatal cerrahi ile daha başarılı sonuçlar alındığı bildirilmektedir. SB tanılı çocukların dikkatle değerlendirilmesi ve çok yönlü, yaşa göre değişen hedeflerle planlanmış rehabilitasyon programları ile yüz güldüren sonuçlar almak mümkündür.

**Anahtar Sözcükler:** Alfa fetö protein; folik asit; meningomyelose; mobilizasyon; spina bifida.