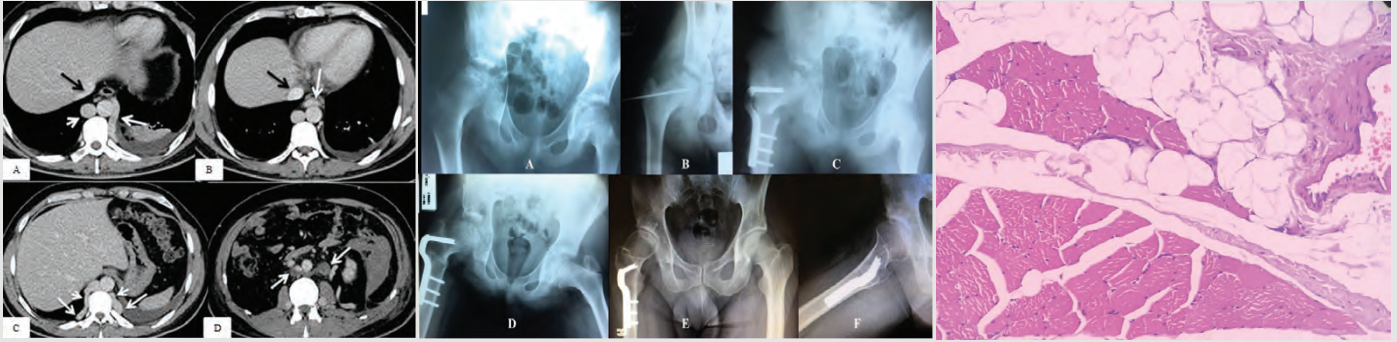


# European Archives of Medical Research

Formerly Okmeydanı Medical Journal

Volume: 38 • Number: 4 • December 2022



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Web: www.galenos.com.tr  
Publisher Certificate Number: 14521  
Publication Date: December 2022

ISSN: 2651-3137 E-ISSN: 2651-3153

International scientific journal published quarterly.

# European Archives of Medical Research

Formerly Okmeydanı Medical Journal

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Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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Slots J. The microflora of black stain on human primary teeth. *Scand J Dent Res*. 1974. Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. *Diagn Interv Radiol* 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

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**Address:** Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 Fındıkzade, İstanbul, Turkey

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# European Archives of Medical Research

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# Effects of Bispectral Index Monitoring During On-pump Coronary Artery Bypass Surgery on Intraoperative Opioid Use and Postoperative Recovery

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## Abstract

**Objective:** Bispectral index (BIS) is a processed electroencephalogram that is extensively used to monitor intraoperative anesthetic depth. There have been studies on the effects of BIS monitoring during cardiac surgery on operative and postoperative results. However, these studies have reported different results. This study evaluated the effects of BIS monitoring on opioid use and postoperative recovery in patients undergoing on-pump coronary artery bypass surgery.

**Methods:** A total of 114 patients who underwent elective on-pump coronary bypass graft surgery were ultimately included in the study and were prospectively randomized into BIS (-) and BIS (+) groups (51 and 63 patients respectively). In BIS (-) group, fentanyl doses were given according to clinical parameters such as hemodynamic changes and follow up pupils. In BIS (+) group, fentanyl doses were adjusted to keep BIS levels between 40 and 50.

**Results:** There were no differences between the two groups with respect to age, sex, body mass index, smoking history and severity of comorbidities. Intraoperative fentanyl use was significantly lower in BIS (+) group; 2676±527.4 and 1632.5±325.5 in BIS (-) and BIS (+) groups respectively (p<0.001). The durations of postoperative intubation (10.5±2.7 vs. 8.05±2.9 h; p<0.001), intensive care unit (ICU) (2.8±0.9 vs. 2.4±0.7 days; p=0.02) and hospital (5.6±3.7 vs. 4.3±1.7 days; p=0.03) stays were also significantly shorter in BIS (+) group.

**Conclusion:** BIS monitoring during on-pump coronary bypass surgery decreases the need for opioid use during surgery. It is also associated with decreased time to extubation and shorter durations of ICU and hospital stays.

**Keywords:** Coronary artery bypass surgery, bispectral index, fentanyl, postoperative clinic effects

## INTRODUCTION

Bispectral index (BIS) is a processed electroencephalogram (EEG) which is derived from the phase coupling of spontaneous EEG (1) and is extensively used to monitor anesthetic depth (1,2). The

measurement of anesthetic depth is important for both titrating anesthetic drugs and for avoiding patient awareness during surgery. It has been suggested that the use of BIS monitoring during surgery decreases hypnotic drug use and results in faster recovery from anesthesia (3). The development of fast



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**Cite this article as:** Gümüş Özcan F, Erkalp K, Şinikoğlu SN, Kayalar N, Polat A, Erentuğ V, Demirgan S, Selcan A. Effects of Bispectral Index Monitoring During On-pump Coronary Artery Bypass Surgery on Intraoperative Opioid Use and Postoperative Recovery. Eur Arch Med Res 2022;38(4):233-237

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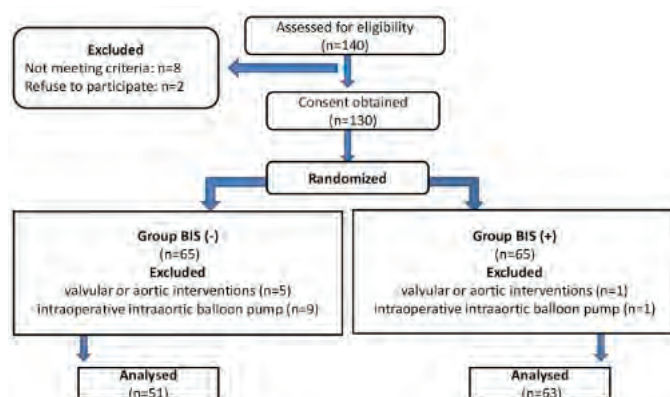
**Received:** 24.11.2020

**Accepted:** 14.10.2021

track cardiac anesthesia techniques has facilitated safe early extubation after cardiac surgery but the role of anesthesia depth monitoring in extubation and length of stay after cardiac surgery has not been well studied (4). There are studies about the effects of BIS monitoring during cardiac surgery on operative and postoperative results such as opioid use, time to extubation and recovery (5). However the evidence for better clinical outcomes is conflicting (1). This study evaluated the effect of BIS monitoring on opioid use and postoperative recovery in patients undergoing isolated on-pump coronary artery bypass surgery.

## METHODS

After obtaining approval of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital, Ethical Committee (ethical approval number: 2011/37) and written informed consent of participants, patients who underwent elective on-pump coronary bypass graft surgery were recruited for this prospective randomized study. The sample size for the study was estimated on the basis of the a previous study (6). Given a 5% two tailed significance level ( $\alpha$ : 0.05) and power of 90%, 50 patients for each group were needed to detect differences in intraoperative fentanyl use between two groups. A total of 140 patients who had undergone elective on-pump coronary bypass graft surgery were recruited for this study. Patients requiring emergency operation, those with severe carotid disease, recent cerebrovascular event and renal/hepatic dysfunction (n=8) and who refused to participate (n=2) were excluded from the study. Patients (n=130) were randomized to two groups [65 patients in group BIS (-), 65 patients in group BIS (+)]. Randomization was performed using a sealed envelope method. Patients who required additional procedures such as valvular or aortic interventions (n=6) and intraoperative intraaortic balloon pump (n=10) were also excluded and 114 patients were ultimately enrolled (Figure 1).



**Figure 1.** Study flow diagram

BIS: Bispectral index

All patients received oral 10 mg diazepam the night before surgery and premedication was done with midazolam 0.07 mg/kg intramuscularly 30 min before anesthesia induction. Routine monitoring with 12 lead electrocardiogram and pulse oximetry was performed. Additionally, the invasive arterial pressure was measured via a right radial artery catheter and recorded continuously. The BISTM monitor (A-2000 Aspect Medical Systems, Inc. Needham, MA, USA) probe was placed on the patients' foreheads (the proximal end of the BIS probe was placed forehead at the midline of the eyebrows, and the distal end was placed on the temple at eye level) and the basal values were recorded. BIS monitoring continued until the end of operation in BIS (+) group.

In both groups standard anesthesia induction technique was used with 7-10  $\mu$ g/kg fentanyl, 0.1 mg/kg midazolam, and 1 mg/kg propofol for induction of all patients. Neuromuscular blockade was achieved by administering vecuronium bromide 0.1 mg/kg. Anesthesia maintenance was achieved with 1.5% sevoflurane, 50% oxygen, and 50% medical air. Sevoflurane concentration was adjusted to 1.5% in both groups to determine the difference between the groups in terms of the amount of fentanyl consumed in the perioperative period. Bolus doses of midazolam (0.1 mg/kg) and vecuronium bromide 0.1 mg/kg were repeated at the onset of cardiopulmonary bypass (CPB) and rewarming period. In BIS (-) group, depending on the clinical parameters such as hemodynamic parameters and follow-up pupils, bolus doses of fentanyl 5  $\mu$ g/kg were administered. Insufficient depth of anesthesia was defined as an increase in systolic blood pressure of more than 15 mmHg, an increase in heart rate of more than 15/min, and concomitant mydriasis in BIS (-) group. However, in the BIS (+) group, bolus doses of fentanyl 5  $\mu$ g/kg were adjusted to keep BIS levels between 40 and 50. Nitroglycerin (1 mg) was given in case where there was 20% increase in mean blood pressure for both groups if the level of BIS was within the normal range (40 and 50) in BIS (+) group, and despite the additional doses of fentanyl in BIS (-) group. Total amount of fentanyl used was recorded.

A double-lumen central venous catheter was inserted into the right internal jugular vein. Controlled mechanical ventilation was instituted to achieve an end-tidal  $\text{CO}_2$  between 35 and 45 mmHg. Temperatures during CPB were maintained between 30 and 32  $^{\circ}\text{C}$ . After median sternotomy, standard methods of extracorporeal circulation and cold blood cardioplegic arrest were employed. Heparin was administered to achieve and maintain an activated clotting time >450 s. After termination of CPB, protamine 1-1.3 mg/100 units heparin was administered. At the end of the operation, the patients were monitored and

transferred to the cardiovascular surgery intensive care unit (ICU) on mechanical ventilation and were extubated after satisfying the criteria for extubation. The team following the patient in the ICU was blinded to the groups.

### Statistical Analysis

Statistical analysis was performed using IBM SPSS statistics version 20 (IBM, Armonk, NY, USA). All data are presented as mean  $\pm$  standard deviation for continuous variables, as numbers with percentage for categorical variables. Differences between categorical variables were tested using the chi-square test and Fisher exact test. In the comparison of two independent groups, the Student t-test was used for numerical variables with normal distribution. A p value of 0.05 or less was considered significant.

## RESULTS

A total of 114 patients who underwent elective on-pump coronary bypass graft surgery were included in this prospective randomized study. Group BIS (-) included 51 patients and group BIS (+) included 63 patients. There was no difference between two groups with respect to age, sex, body mass index, smoking history, and severity of comorbidities such as cardiac, pulmonary, vascular and renal disease (Table 1).

The number of bypass grafts was higher and durations of aortic cross clamp and CBP were slightly longer in BIS (+) group although not significantly (Table 2). The inotrope use were not different between groups. The duration of operation (as measured by total anesthesia time) was statistically longer in BIS (+) group. In spite of that, intraoperative fentanyl use was significantly lower in BIS (+) group compared to the BIS (-)

Variable	Group BIS (-) n=51	Group BIS (+) n=63	p value
Age (years)	59.3 $\pm$ 11.3	62.06 $\pm$ 10.1	0.1
Ejection fraction	50.14 $\pm$ 8.3	49.9 $\pm$ 8.1	0.8
BMI	27.8 $\pm$ 4.1	28.9 $\pm$ 4.2	0.1
Sex (n)			
Male	38	416	0.5
Female	13		
Hypertension	33 (64.7%)	39 (61.9%)	0.2
Smoking	29 (56.9%)	32 (50.8%)	0.3
Diabetes mellitus	24 (47.1%)	26 (41.3%)	0.1
COPD	20 (39.2%)	22 (34.9%)	0.2
Previous MI	24 (47.1%)	20 (31.7%)	0.1
Peripheral arterial disease	3 (5.9%)	8 (12.7%)	0.4

BMI: Body mass index, BIS: Bispectral index, COPD: Chronic obstructive pulmonary disease, MI: Myocardial infarction

group (2676 $\pm$ 527.4 vs. 1632.5 $\pm$ 325.5,  $p<0.001$ ). The durations of postoperative intubation, ICU and hospital stays were also significantly shorter in BIS (+) group ( $p<0.001$ ,  $p=0.02$ ,  $p=0.03$  respectively, Table 2).

There was no mortality in any patient in the study. There was no difference in terms of drainage or complications. Atrial fibrillation developed in 2 patients in each group and sternal wound drainage was observed in 1 patient in BIS (+) group. Reexploration for bleeding was seen in 1 patient in BIS (-) group. But this patient was taken to the operating room 2 h after extubation and therefore, first extubation time was used for analysis and did not affect results.

## DISCUSSION

Patients undergoing cardiac surgery are a complex group with multiple comorbidities and present a special challenge for anesthesiologists. Extensive monitorization is usually necessary with sophisticated technologies (2). Brain monitoring and assessing depth of anesthesia are important order to decrease the incidence of awareness during surgery, to reduce time to awakening and overall anesthetic consumption and to provide surrogate information on cerebral perfusion. Several parameters have been used to assess the depth of anesthesia which include hemodynamics (7), pupillary reflex, and skin conductivity (8). The most reliable variables were derived from the EEG (9). The BIS is a processed EEG that has been investigated in different studies and is presently the most extensively validated measure of depth of anesthesia (9). The BIS reports a number from 0 to

Variable	Group BIS (-) n=51	Group BIS (+) n=63	p value
Duration of operation (min)	191.1 $\pm$ 45.1	217.2 $\pm$ 49.7	<b>0.008</b>
Duration of ACC (min)	52.9 $\pm$ 25.8	62.3 $\pm$ 28.01	0.06
Duration of CPB (min)	89.08 $\pm$ 33.4	101.9 $\pm$ 38.8	0.06
Number of coronary grafts	2.6 $\pm$ 0.8	2.9 $\pm$ 0.8	0.06
Fentanyl used ( $\mu$ g)	2676 $\pm$ 527.4	1632.5 $\pm$ 325.5	<b>&lt;0.001</b>
Duration of intubation (hrs)	10.5 $\pm$ 2.7	8.05 $\pm$ 2.9	<b>&lt;0.001</b>
Duration of ICU stay (days)	2.8 $\pm$ 0.9	2.4 $\pm$ 0.7	<b>0.02</b>
Duration of hospital stay	5.6 $\pm$ 3.7	4.3 $\pm$ 1.7	<b>0.03</b>
Drainage	565.6 $\pm$ 281.8	559.1 $\pm$ 215.9	0.05
Mortality	None	None	None

ACC: Aortic cross clamp, CPB: Cardiopulmonary bypass, min: Minutes, hrs: Hours, BIS: Bispectral index

100; 100 represents an awake state and 0 represents complete EEG inactivity.

The use of BIS monitoring during general anesthesia was associated with significantly reduced incidence of awareness (10) and many authors showed a correlation between BIS and level of awareness (11,12). Several studies have demonstrated that BIS monitoring can reduce anesthetic use and, consequently, the time to extubation and other recovery parameters in non-cardiac surgery (13,14). Taş et al. (15) showed that BIS monitorization can help avoid excessive anesthetic agent use and to faster recovery from anesthesia in patients undergoing thyroidectomy. However, in several other studies, BIS monitoring was not associated with better postoperative outcomes (16). In the B-Aware (17), B-Unaware (18), and BAG-RECALL (19) trials, the use of BIS monitoring was not associated with a reduction in the amount of anesthesia administered or a decreased hospital length of stay.

There are studies have examined the use of BIS monitoring in cardiac surgery (5) and there is still controversy about the effects of BIS monitoring on postoperative recovery. Villafranca et al. (20) performed a secondary analysis of the BAGRECALL trial and demonstrated that compared with management based on end-tidal anesthetic concentration, anesthetic management based on BIS guidance does not strongly increase the probability of an earlier extubation in patients undergoing fast-track cardiac surgery. They suggested that the decision for extubation was more influenced by patient characteristics and perioperative course than the assignment to BIS or end-tidal anesthetic concentration monitoring. Similarly, Vance et al. (4) showed no difference in time to extubation between BIS-guided and mean alveolar concentration-guided anesthetics in patients undergoing cardiac surgery. Moreover, their results showed no statistically significant differences in ICU and total post-operative hospital length of stay.

In this study, our results revealed a significant difference in intraoperative opioid use. Additionally, we observed statistically significant differences in time to extubation and durations of ICU and hospital stays. This difference is mainly the result of different anesthetic management techniques between our study group and previous studies. Most of these studies used only mean alveolar concentration in patients who were not monitored by BIS. In our study inhalation anesthetic technique was similar in two groups, whereas intravenous opioid use was based on BIS monitoring. Therefore, instead of hemodynamic parameters, BIS values were used to guide intravenous opioid usage and a significant difference was observed as a result.

Another important factor may be a more homogenous patient group that includes only coronary artery bypass surgery. Other studies on patients cardiac surgery included all cardiac surgical procedures (4,5,20).

There are many factors that can affect postoperative recovery following cardiac surgery, including the development of low cardiac output, excessive bleeding, inotrope use, pre-existing comorbidities, prolonged surgical time, and excessive depth of anesthesia. In this study, the two groups were well matched in key areas. There were no significant differences between the groups in terms of preoperative comorbidities, ejection fraction, age, and sex (Table 1). There was also no difference in drainage, inotrope use or postoperative complications. The duration of operation was longer in BIS (+) group. Therefore, management of opioid use based on BIS monitoring remains an important factor for better postoperative results in our patients. Our study show that beneficial effects of BIS monitoring on both extubation times and ICU and total post-operative hospital length of stay.

### Study Limitations

There were some limitations to our study. First, although other factors affecting postoperative recovery were similar in our patient group, studies with a higher number of patients must evaluate BIS monitoring as an independent factor for early extubation. Second, different anesthetic management strategies should be compared to determine the best management of cardiac surgery patients.

## CONCLUSION

BIS monitoring during on-pump coronary bypass surgery decreases the need for opioid use. It is associated with decreased time to extubation and shorter durations of ICU and hospital stays. Further studies are recommended to evaluate BIS monitoring as an independent factor for early extubation and faster postoperative recovery after cardiac surgery.

### Ethics

**Ethics Committee Approval:** University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital, Ethical Committee (ethical approval number: 2011/37).

**Informed Consent:** Consent was received.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: F.G.Ö., A.P., K.E., Design: F.G.Ö., A.S., V.E., Data Collection or Processing: F.G.Ö., A.P., Analysis or Interpretation: F.G.Ö., N.K., S.D., Literature Search: F.G.Ö., N.K., S.D., Writing: F.G.Ö., N.K., S.N.Ş.



**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# The Clinical and Radiographic Results of a Mean 23 Year Follow-up Period of Children with Legg-Calve-Perthes Disease Applied with Femoral Varus Derotation Osteotomy: What are the Factors Affecting the Long-term Results?

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## Abstract

**Objective:** The aim of this study was to evaluate the long-term results of cases applied with femoral varus derotation osteotomy (FVDO) in our clinic because of Legg-Calve-Perthes disease (LCPD), and to determine the factors affecting the results.

**Methods:** This retrospective, single centre study included 22 patients (19 males, 3 females) who had undergone FVDO for a diagnosis of LCPD, had regular clinical and radiological follow-up, and could be contacted by telephone. The patients were evaluated with the Waldenström and Lateral Pillar classifications, the Harris Hip score, the Stulberg Hip score, and the short-form-36, and the results were compared.

**Results:** Evaluation was made of 22 patients, comprising 19 males and 3 females with a mean age of 31.5±6.9 years, operated on because of LCPD. The mean follow-up time was 23±6.2 years and the mean age at first presentation was 6.5±2.6 years. Lateral pillar class C was determined as an indicator of a poor outcome in patients in the Waldenström fragmentation stage. The outcomes were better in patients who were diagnosed at the age of <8 years and operated on <10 years in the early stages of the disease.

**Conclusion:** Although FVDO is an effective surgical method in LCPD cases, the chance of success is higher when diagnosis is made before 8 years old, and surgery is applied before the age of 10 years in the initial stage according to the Waldenström classification. Therefore, the importance of early and diagnosis and treatment in LCPD must be emphasised.

**Keywords:** Femoral varus-derotation surgery, Legg-Calve-Perthes disease, osteonecrosis

## INTRODUCTION

Legg-Calve-Perthes disease (LCPD) is a juvenile hip disorder, which progresses at later stages with pain in the hip joint and findings of early arthrosis (1). Incidence of the disease is 0.5-21/100.000, and it is seen 4-5 fold more in boys than girls, and most often in the 4-8 years age group (2). Although the etiology of the disease is not fully known, reasons have been suggested such as trauma, clotting disorders, factor V Leiden mutation, hyperactivity, low socio-economic level, exposure

to cigarette smoke, low birthweight, genetic predisposition, and retarded skeletal age. Patients presenting with complaints such as limping, hip, and anterior knee pain are evaluated with direct pelvis anterior-posterior radiographs. The main principle in treatment is acetabular coverage of the sensitive femoral head with impaired vascularization, to increase the blood flow by decreasing the increasing intra-articular pressure, and thereby obtain a spherical femoral head compatible with the acetabulum (3). The leading surgical methods reported to date



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**Received:** 30.07.2021  
**Accepted:** 07.11.2021

**Cite this article as:** Teksan E, Aydın H. The Clinical and Radiographic Results of a Mean 23 Year Follow-up Period of Children with Legg-Calve-Perthes Disease Applied with Femoral Varus Derotation Osteotomy: What are the Factors Affecting the Long-term Results? Eur Arch Med Res 2022;38(4):238-243

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are Salter osteotomy, combined osteotomy (femoral and pelvic osteotomy), chiari osteotomy, shelf arthroplasty, and femoral varus derotation osteotomy (FVDO).

Although short- and mid-term follow-up results of the surgical treatment of LCPD have often been reported in literature, there are very few studies that have reported the long-term results of surgical treatment (4-6). This study aimed to evaluate the long-term results of cases applied FVDO in our clinic because of LCPD and to determine the factors affecting the results.

## METHODS

This retrospective study was approved by the Karadeniz Technical University Faculty of Medicine Institutional Review Board (IRB protocol number: 2018/149) and the requirement for informed consent was waived. We retrospectively examined 26 hips of 22 patients who were applied with FVDO for a diagnosis of LCPD between 1983 and 2003, when they were aged 6-12 years. The patients included had at least 15 years of follow-up, attended final follow-up examinations, had direct radiographs available and were not missing any data in the records. Patient records were retrospectively examined. The Waldenström and Lateral Pillar classifications were applied by evaluating the preoperative clinical and demographic data together with the direct radiographic images (Table 1).

Patients were then called by telephone to undergo a follow-up examination. Those who attended were evaluated with the Harris Hip score, the Stulberg Hip score, Tonnis osteoarthritis grading, and parameters affecting activities of daily living [short-form-36 (SF-36)]. Limb length discrepancy was defined with the measurement of the distance between the spina iliaca anterior superior and the medial malleolus.

All the patients were operated on with the intertrochanteric closed wedge derotation varus osteotomy technique. Postoperatively, a pelvipedal plaster cast was applied as far as the toes, with the hip in 30° abduction and 10-15° internal rotation. The cast was removed after approximately 9 weeks according to the X-ray findings. Subsequently, weight-bearing was permitted and joint range of motion (ROM) exercises were initiated.

To compare the effect of the preoperative lateral pillar and Waldenström classifications on the clinical and radiographic results, the patients were separated into groups of age at diagnosis and age at operation. The groups were defined with reference to similar studies in the literature (5,6) as age at diagnosis of <8 years and ≥8 years, and age at operation of <10 years and ≥10 years.

**Table 1. Demographic and preoperative radiographic characteristics of the patients**

Variables	Data
Age (years)	31.5±6.9
<b>Gender</b>	
- Female	3 (13.6)
- Male	19 (86.4)
Age at onset of complaints	6.5±2.6 (1.0-11.0)
<b>Age at diagnosis</b>	
- <8 years	14 (63.6)
- ≥8 years	8 (36.4)
Follow-up period (years)	23±6.2 (15.0-35.0)
Mean age at operation (years)	8.2 (6.0-12.0)
<b>Age at operation</b>	
<10 years	13 (59.1)
≥10 years	9 (40.9)
<b>Operation side</b>	
Right	8 (36.4)
Left	10 (45.5)
Bilateral	4 (18.2)
<b>Waldenström classification (hip)</b>	
Initial	7 (26.9)
Fragmentation	19 (73.1)
<b>Lateral pillar classification (hip)</b>	
A	2 (7.7)
B	10 (38.5)
B/C	2 (7.7)
C	12 (46.1)

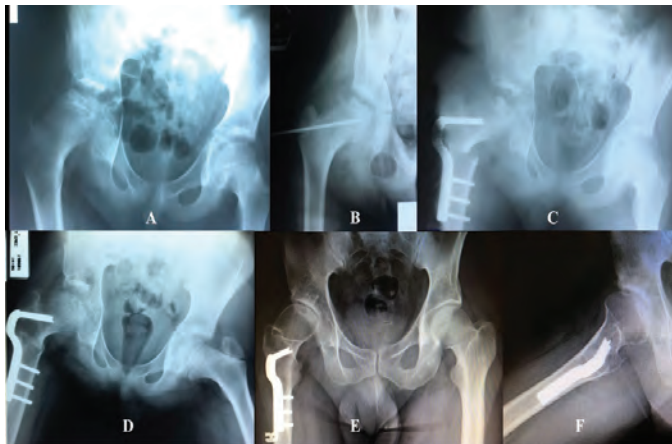
## Statistical Analysis

In the comparison of variables not showing a normal distribution, the Mann-Whitney U test and the Kruskal-Wallis test were applied as non-parametric tests. In the evaluation of repeated measurements showing a normal distribution, the Paired t-test was applied to dependent groups. Fisher's exact test or the chi-square test were applied in the comparison of categorical data. A value of  $p < 0.05$  was set as statistically significant.

## RESULTS

According to the Harris Hip score at the final follow-up examination, the mean score was 86.8 and none of the patients had a poor result (0-40) (evaluation range, 1-100). One hip was evaluated as fair (41-60), one as good (61-70), 5 as excellent (71-85) and 19 as excellent (86-100). In the Stulberg scoring, 15 hips were evaluated as a good outcome (11 hips grade 1, 4 hips grade 2) and 11 hips were evaluated as a poor outcome (4 hips grade 3, 4 hips grade 4, 3 hips grade 5) (Figures 1, 3).

Of the 26 hips, 12 (46.1%) were classified as lateral pillar grade C, with shortness determined in the affected extremity.



**Figure 1.** Preoperative image of a 10-year old patient in the fragmentation stage, lateral pillar C(A). Intraoperative radiograph of the patient at 11 years old showing the guide K-wire used for osteotomy (B). Early postoperative radiograph (C). Follow-up radiograph at 13 years old (D). Final follow-up examination radiographs (E, F) showing flattening of the femoral head and changes in the acetabulum. The result was aspherical compatible, Stulberg grade 3



**Figure 2.** Radiograph of 4-year-old patient at Waldenström grade 1, lateral pillar grade B, showing the metaphyseal defect below the epiphysis (A). Frog leg position view (B). Early postoperative radiograph (C). Follow-up radiographs at age 9 years(D) and 13 years (E). Final follow-up examination radiograph (F) showing full femur head and acetabulum congruence. Spherical compatible, Stulberg grade 1

According to the Tonnis grading, no findings of degenerative osteoarthritis were determined in 12 hips, findings of mild osteoarthritis were seen in 7 hips, and grade 2 or 3 degenerative osteoarthritis was determined in 7 hips (5 hips grade 2, 2 hips grade 3). The mean SF-36 score was calculated as 78.3 (maximum: 100) (Table 2).

The patients were classified according to age at diagnosis (<8 years and ≥8 years) and age at operation (<10 years and ≥10 years), and the preoperative lateral pillar and Waldenström classifications were compared with the final follow-up clinical and radiographic results (Table 3).

The Harris Hip score in patients diagnosed <8 years was statistically significantly higher than that of the patients diagnosed at ≥8 years (p=0.007). Of the 26 hips diagnosed <8

years, 14 (77.8%) had a good Stulberg score (grade 1-2) and 1 (12.5%) of those diagnosed at ≥8 years had a good result (p=0.003). According to the Tonnis grading, significantly fewer of the patients diagnosed at <8 years had findings of degenerative osteoarthritis (p=0.004).

According to the age at operation, the Harris Hip score was significantly lower in the group operated on at ≥10 years (p=0.016). The rate of patients with a good Stulberg score (1-2) was significantly higher in the <10 year age operation group compared to the ≥ decade age at the operation group (76.5% vs. 22.2%) (p=0.014). A higher rate of degenerative osteoarthritis was determined in the ≥ decade age at the operation group compared to those operated on at <10 years (p=0.023). No difference in was determined between the two groups of age at operation with respect to the Stulberg score (p=0.057). The SF-36 score was found to be higher in the < decade age at the operation group than those operated on at ≥10 years (81.31±16.4 vs. 74.02±18.2) but the difference was not statistically significant (p=0.209).

Harris Hip scores were generally higher in patients at the initial stage according to the Waldenström classification, the Stulberg score was lower, and the rate of good results was statistically significantly higher. Of the 14 hips with lateral pillar grade A, grade B, and grade B/C, 12 (85.7%) were evaluated as excellent according to the Harris Hip score, and 7 (58.3%) of the 12 hips with grade C obtained an excellent result. The rate of excellent results according to the Harris Hip score was lower in the lateral pillar grade C cases, but not statistically significant (p=0.902). The rate of those with a good Stulberg score in the lateral pillar C group was significantly lower than that in the other groups (p=0.012).

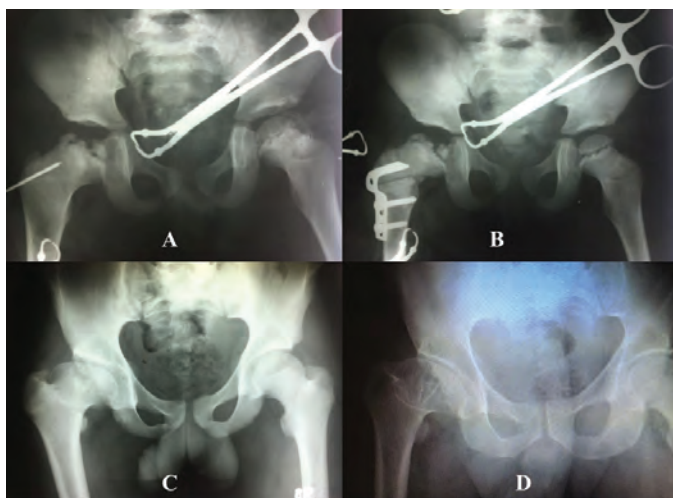
Variables	Data
<b>Tonnis osteoarthritis classification (hip)</b>	
- 0	12 (46.1)
- 1	7 (26.9)
- 2	5 (19.2)
- 3	2 (7.7)
<b>Harris Hip score (0-100)</b>	
- Poor	0 (0)
- Fair	1 (3.8)
- Good	1 (3.8)
- Very good	5 (19.2)
- Excellent	19 (73.1)
<b>Stulberg score (hip)</b>	
- 1	11 (42.3)
- 2	4 (15.4)
- 3	4 (15.4)
- 4	4 (15.4)
- 5	3 (11.5)
Short-form-36 score (mean)	78.3±17.2



**Table 3. Analysis of the clinical and radiological factors affecting the long-term results**

		No of hips	Harris	p	Stulberg grade 3-5	p	Degenerative osteoarthritis	SF-36		
			Mean ± SD					p	Mean ± SD	p
Age at diagnosis	<8 y (n=14)	18	90.6±9.9	0.002	4	0.003	2	0.014	78.1±19.0	0.285
	≥8 y (n=8)	8	78.6±8.6		7		5		75.3±12.8	
Age at operation	<10 y (n=13)	17	90.5±10.4	0.004	4	0.014	2	0.028	78.9±16.8	0.376
	≥10 y (n=9)	9	80.1±8.8		7		5		74.0±18.3	
Lateral pillar grade	A	2	91.5±6.4	0.076	0	0.017	0	0.103	95.0±1.4	0.076
	B	10	92.0±7.2		2		1		83.3±14.4	
	B/C	2	91.5±2.1		0		0		87.1±6.9	
	C	12	81.1±12.5		9		6		67.6±16.8	
Waldenström classification	Initial	7	95.1±4.3	0.003	1	0.010	0	0.134	93.6±3.0	<0.001
	Fragmentation	19	83.4±11.1		11		7		71.2±16.2	

SD: Standard deviation, SF-36: Short-form-36 score



**Figure 3.** Preoperative radiograph of an 11-year old male patients with Waldenström fragmentation grade and lateral pillar grade C (A). Early postoperative image (B). Follow-up radiograph at age 30 years showing flattening of the femoral head and shortness in the neck (C). Final follow-up examination radiograph at age 46 years (D) showing flattening of the femoral head and shortness in the neck. Tönnis grade 1 osteoarthritis is present. Partial congruence with the acetabulum was achieved, aspherical compatible, Stulberg grade 4.

### DISCUSSION

The aim of treatment for LCPD is to prevent the possibility of coxarthrosis developing by obtaining a normal or near normal hip joint. When the disease was first identified, bed rest and devices to avoid weight-bearing were used (7), and this later changed to abduction plaster cast and orthoses. However, over time studies of conservative treatment have shown that orthosis treatment is not sufficiently effective (8). As the results obtained with conservative treatment were not sufficiently satisfactory, this led to an increased tendency for surgery.

In a multicentre, prospective study, the clinical and radiographic results of the clinical treatment of LCPD were evaluated in 451 hips of 438 patients. The results of patients diagnosed at more than 8 years and with lateral pillar B or B/C were better than the surgical treatment results in the literature, but it was emphasized that those with lateral pillar C had a worse result independent of age (9). In this study, the mean follow-up period was 23 years and the mean age at surgery was 7.5 years. At the final follow-up examination, the mean patient age was 31.5 years, and 9 of the 11 patients with a poor Stulberg score had lateral pillar grade C. Of the 12 hips with lateral pillar grade B and grade B/C, 2 had a poor outcome according to the Stulberg score. Thus, it can be concluded that surgical treatment in this group was at least as successful as conservative treatment. Similarly, in patients with lateral pillar grade C, a direct relationship was determined by a poor outcome (p=0.018).

The Stulberg score of patients in the initial Waldenström grade was found to be statistically significantly lower than that of patients diagnosed in the fragmentation grade. In this context, organizing treatment in the initial stage immediately after a simple pelvis radiograph taken of a child presenting with limping, which is an early clinical sign of the disease, provide the clinician with a great advantage for treatment with better results.

The application of the principle of surgical coverage was started in 1952 by Soeur and De Racker (10) with the application of proximal FVDO. In 1962, Salter (11) brought a new dimension to the coverage principle by performing innominate osteotomy. Sponseller et al. (12) compared FVDO and innominate osteotomies, and despite no functional difference determined,



recommended that FVDO be preferred in patients with limb length discrepancy when the growth plate was closed. The coverage principle can be applied without problems in mild and moderate degree patients, but a series of problems have been encountered in severe cases (13,14). Even more shortening of the extremity in patients applied with proximal FVDO, and the Salter innominate osteotomy not providing sufficient coverage in patients affected to an advanced degree constitute problems in surgical treatment (12). In this study, 14 (63.6%) of 22 patients were lateral pillar grade C and shortness was determined in the affected extremity. As extremity shortness is related to limping, this result can be said to be the most important disadvantage attributable to the FVDO operation.

The Stulberg score results were evaluated as good (grade 1-2) in 58% of the hips evaluated in this study and poor (grade 3-5) in 42%. According to the Harris Hip scores, no patient had a poor result. The mean SF-36 value was  $78.33 \pm 17.15$ . Despite the 11 poor results according to the Stulberg score, the reason that their were no poor results in the Harris Hip score can be explained by the fact that a radiographic result may be reflected differently clinically, the pain threshold of the local population is high, and they have high general resistance and muscle strength.

In this study, patients diagnosed at  $<8$  years and operated on at  $<10$  years, better results were determined with respect of the Harris Hip score, Tonnis grade and SF-36 values. The Stulberg score of the patients diagnosed at  $<8$  years was significantly better than that of patients diagnosed at  $\geq 8$  years ( $p=0.003$ ), but no significant difference was determined between those operated on at  $<10$  years or  $\geq 10$  years ( $p>0.05$ ). It can be concluded that this result was due to close follow-up and muscle-joint exercises applied to patients with an early diagnosis, that they responded well to traction and anti-inflammatory treatment, and this directly affected the surgical outcome.

However, a significant difference was determined between the patients operated on at  $<10$  years and  $\geq 10$  years regarding the Harris Hip score in contrast to the Stulberg score, the Harris Hip score was statistically significantly higher in those operated in  $<10$  years ( $p<0.05$ ). Generally, this scoring system evaluates the hip joint and the effect of the joint dynamics on walking and normal life, and is considered clinically separate from the Stulberg classification, which is a radiological evaluation criteria. The quality of life of a patient who has no pain, can walk without limping, and can easily perform daily tasks, including heavy work, will be just as high in terms of this disease. Consequently, the evaluation of radiological worsening will probably be more valuable in long-term follow-up.

Similar to the current study, Aydin et al. (6) conducted another multicentre study in Turkey and evaluated 21 hip joints applied with FVDO because of LCPD. In that study, the male-female ratio was 18:2, the mean age at surgery was 8.8 years, and the mean follow-up period was 25.1 years. Better results were determined in patients aged  $<10$  years when operated on, and the clinical and radiological results were worse and degenerative osteoarthritis was more frequent in those with lateral pillar grade C in the preoperative evaluation. Degenerative osteoarthritis was determined in 33% of the patients.

Degenerative osteoarthritis is the most significant complication of LCPD and affects the long-term outcomes (15). Advanced degenerative osteoarthritis will cause severe hip pain, eventually resulting in total hip prosthesis for the patient, and will be a significant factor determining the quality of life of the patient in the long term. In this study, 1 patient was progressing to arthroplasty and 4 (18.2%) had hip pain that was not severe. These degenerative osteoarthritis had developed in 14 (53.9%) of the 26 hips would appear to be a worse result than that reported by Aydin et al. (6). However, of the 14 hips seen having osteoarthritis, 7 were Tonnis grade 1 (mild). Nevertheless, it is difficult to comment on the results as previously reported studies have excluded the same grade and age groups, and the skills of different surgeons can directly change operation outcomes, so this remains open to debate.

### Study Limitations

A primary limitation of this study was the lack of a control group. Therefore, in the evaluation of the surgical treatment results, there can be no comparison with conservative treatment or other surgical treatments. Although the number of patients was relatively low, when the 23 year follow-up period is considered, it can be concluded that the number of patients is reasonable. This is one of the very few studies in the literature to have included the long-term follow-up results of more than 20 years.

### CONCLUSION

In conclusion, better results were obtained in patients diagnosed at  $<8$  years and when operated on at  $<10$  years. Therefore, the importance of the early diagnosis and treatment of LCPD must be emphasized. When deciding for treatment of patients, it must be considered that in FVDO treatment, there are fewer painful hips, less osteoarthritis, and lower rates of progression to arthroplasty compared with conservative treatment, especially in lateral pillar grade C and patients aged more than 8 years at the fragmentation stage.

## Ethics

**Ethics Committee Approval:** Karadeniz Technical University Faculty of Medicine Institutional Review Board (IRB protocol number: 2018/149).

**Informed Consent:** Informed consent was waived.

**Peer-review:** Externally and internally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: E.T., H.A., Concept: E.T., H.A., Design: E.T., H.A., Data Collection or Processing: E.T., H.A., Analysis or Interpretation: E.T., H.A., Literature Search: E.T., H.A., Writing: E.T., H.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# The Effect of Cross Clamp Time on Neurocognitive Function in Coronary Artery Bypass Surgery

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## Abstract

**Objective:** This study evaluates the importance of cross clamp time (CCT) on neurocognitive function in coronary artery bypass graft at an early postoperative period.

**Methods:** The standardized mini mental state examination (SMMSE) is used to determine the neurocognitive function. This is a prospective study on 100 consecutive patients within a certain time interval in a single clinic.

**Results:** During the study period 100 participants are analysed by SMMSE, preoperatively and postoperatively. The CCT under 120 min had no significant impact on neurocognitive function ( $p>0.05$ ). Mean age ( $57.8\pm 9.7$ ). 82% men, 18% women. Median SMMSE point:  $29\pm 0.8$  (preoperative),  $29.2\pm 0.8$  (postoperative) ( $p>0.05$ ). CCT is  $62.6\pm 27.8$  min and cardiopulmonary bypass time is  $82.3\pm 32.4$  min in this study.

**Conclusion:** We have found no correlation between CCT (median:  $62\pm 27$  min) and neurocognitive function. The study implies that surgeons can relax in CCT under 120 min in terms of neurocognitive disorder.

**Keywords:** Aortic cross clamp, neurocognitive function, standardized mini mental state examination, coronary artery bypass graft surgery

## INTRODUCTION

Cardiopulmonary bypass (CPB) support during cardiac surgery is unique because blood is exposed to the foreign surface and continuously recirculated throughout the body (1).

This inflammatory response to CPB initiates a powerful thrombotic stimulus. Circulation of vasoactive and cytotoxic substances affects every organ and tissue within the body (1).

The technological advances -arterial filter systems, perfusion monitors, oxygenators, tubings- have decreased the mortality and morbidity related to coronary artery bypass graft (CABG) since modern extracorporeal circulation was first used by Gibbon (2,3). Nevertheless, neurological issues are still part of serious problems. The great majority of neurological disorders related to CABG are CPB and manipulation of the aorta (4). Hypoperfusion and systemic inflammation response can occur

during CPB. Cerebral microemboli may have occurred because of manipulation and cross clamping of the aorta (5).

There are two types of neurological injury after CABG. Type 1: Transient ischemic attack, encephalopathy, stroke, and coma. Type 2: Neurocognitive decline.

The duration of cross clamping of the aorta affects the neurocognitive function because the extracorporeal CPB activates the coagulation cascade and inflammatory response (6). Neurocognitive decline impresses the daily life of the patient that is detectable by relatives (7).

Neurocognitive decline related to CABG is enhanced by aortic cross clamp (8). Although some studies observe small neurocognitive benefits in off-pump CABG, most RCTs prove the advantage of using an aortic clamp (8).



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**Cite this article as:** Albay E, Elçi ME, Olsun A, Kahraman MA, Ketenci B, Koçoğulları CU. The Effect of Cross Clamp Time on Neurocognitive Function in Coronary Artery Bypass Surgery. Eur Arch Med Res 2022;38(4):244-247

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 15.06.2021  
**Accepted:** 21.11.2021

Reducing the aortic manipulation is the main concept of the single cross-clamp CABG strategy. It minimizes cerebral embolic events, so does neurocognitive descent (9).

Bucerius et al.'s (10) study remarked that 10% of stroke events occurring in CABG have a CPB duration over 120 min. cross clamp time (CCT) >88 min was a risk factor for neurological complications in an other study (11).

This study was designed to determine the effect of CCT on neurocognitive function. We analyzed cross clamp duration for understanding whether it affects the neurocognitive function of individuals or not.

## METHODS

A prospective study was chosen. Single clinic Dr. Siyami Ersek Thoracic Cardiovascular Surgery Training and Research Hospital-attended to this research.

One hundred consecutive individuals who underwent CABG surgery between February 2015-July 2015 were enrolled in the investigation and approved by the University of Health Sciences Turkey, İstanbul Dr. Siyami Ersek Thoracic Cardiovascular Surgery Training and Research Hospital institutional Ethics Committee (BŞH.FR.40, decision date: 11.02.2015). Written informed consent was obtained from the patients before the inclusion of the study. Demographic and clinical datas were obtained for each patient. Standard assessments, including physical examinations, chest X-ray, laboratory tests were performed. The criteria for selecting individuals: Non-concomitant surgery, non-carotid artery disease, non-valve disease, non-cardiomyopathy.

The primary inclusion criterion was using aortic cross clamp in coronary artery bypass surgery.

Conventional CABG surgeries were performed using either left internal mammary artery (LIMA) as the bypass conduit or reversed saphenous vein grafts from the legs. Pedicled LIMA graft to the LAD and reversed saphenous vein grafts to other coronary arteries were anastomosed. Proximal anastomoses were done using a single clamp technique. Operations are carried out by many different surgeons with similar techniques in the same clinic.

CPB was instituted with a single, two-stage right atrial cannula, an ascending aortic perfusion cannula, and an ascending aortic cardioplegia cannula. Arterial line filters, membrane oxygenators, moderate hemodilution (hematocrit, 20-24%) techniques,  $\alpha$ -stat acid-base balance were used in all operations. Pulsatile flows (2-2.4 L/min/m<sup>2</sup>) were used. Mean arterial pressures were 60-80 mmHg. Target systemic temperatures were 28-32 °C.

Warm blood cardioplegia was delivered. Initially high-potassium cardioplegia (KCl 100 mmol/L, 1000 mL) was administered at 300 mL/min into the aortic root at an aortic pressure of 100 mmHg to achieve cardiac arrest. During cross clamp, intermittent (20 min) perfusion was used. The same anesthetist group was enrolled in all operations. Premedication was administered with midazolam (3 mg intramuscular). Anesthesia was induced with either fentanyl (500 µg), propofol (0.5 to 1.0 mg/kg) or rocuronium (0.6 mg/kg). Sevoflurane and propofol were used for maintenance of anesthesia.

Age, gender, education status were registered. Ejection fractions <40% and were excluded. Respiratory function tests of individuals were normal. Participants who had abnormal blood test results preoperatively were excluded.

Because preoperative renal deficiency is an independent risk factor for neurological disorders (12), we excluded these patients from the current study. Simões et al. (13) remarked in their study that chronic kidney disease is the most potent risk factor for neurocognitive disorder.

Neurocognitive function has been assessed by measuring standardized mini mental state examination (SMMSE). SMMSE is one of the most well-known tests for assessing neurocognitive function (14).

The SMMSE was developed to provide scoring instructions and clarify indistinct MMSE to raise trusty and lower variability. The SMMSE assesses neurocognitive function, including orientation, memory, attention, calculation, remembrance, language.

## Statistical Analysis

Number Cruncher Statistical System 2007 program was used for statistical analysis. Descriptive statistical methods such as mean, standard deviation, median, frequency, ratio, and Student's t-test, Mann-Whitney U test, Wilcoxon test were used for evaluating study datas.

Spearman correlation analysis was performed for assessing measurement relations ( $p < 0.05$ ).

The subjects who had aortic calcification seen on chest X-ray and have carotid stenosis >50% preoperatively were excluded. Such as urgent surgeries were excluded. Urgent cardiac surgery is an independent risk of stroke (10).

Redo CABG is an independent risk factor for stroke (10). Native structure deteriorates in the first surgical intervention, so that the manipulation gets more difficult in redo surgery. Because of these, the surgery gets longer and embolic events get more. The current study did not evaluate redo participants.

## RESULTS

The mean age of individuals is  $57.8 \pm 9.7$ . 82% men, 18% women. The mean CCT is  $62.6 \pm 27.8$  (Table 1).

Table 2 compares the results obtained from the SMMSE score of individuals pre and post-operatively according to cross clamp duration. Also the results of the correlation analysis are shown. What stands out in Table 2: There is no significant difference between CCT and neurocognitive function when the cross clamp duration was  $62.6 \pm 27.8$  min, mean standard deviation.

The CPB time is  $82.3 \pm 32.4$  min.

We analyzed the difference in age, CCT, pre-op and post-op SMMSE scores between men and women. Table 3 shows that no significant differences were found between men and women.

No significant correlation was found between CCT and the age of the individuals [ $r$  (Spearman correlation parameter): 0.02 and  $p < 0.05$ ].

## DISCUSSION

Although the improvement in open heart surgery especially in heart lung machines, neurocognitive function disorders are

still one of the most affective problems for patients with both morbidity and mortality.

Neurocognitive complications are multifactorial. Micro and macroembolic injury, abnormal cerebral perfusion, inflammatory, and neurohumoral response, pre-morbid disease, fragility are all influential factors related to neurocognitive function. No matter what the reason, the result is the same: Neuronal hypoxia and ischemia. Of course, CPB duration is powerful for neurocognitive function however our study is focusing on the CCT effect. Furthermore the greater CCT is the greater CPB duration. Technological advances protect the neuronal system as pointed out in the text. Although filter systems protect most majority of emboli, we should not manipulate aorta more not to provoke mobilizing microembolism and hypoperfusion of brain. Evidence suggests that off-pump CABG is associated with reduced perioperative stroke in higher-risk patients, including those with atheromatous disease of the ascending aorta.

Emboli during on-pump CABG can occur from a variety of sources such as aortic cannulation, aortic clamp removal, or bypass circuit. Therefore each source need further research. Our study is about one of them.

Dissimilar pulsatile perfusion during CPB may account for the appearance of diffuse brain edema. Systemic inflammation is an other influential factor on cerebral function.

No neuroprotective substances for cardioplegic solutions were used, as mentioned in the methods section. We could not have any further decisions about the effect of neurocognitive function related to content of cardioplegia.

Preoperative renal dysfunction is an important independent predictor of in-hospital and late mortality in adult patients undergoing cardiac surgery (12). Excluding such patients from our study made the study clearer. So that we could better focus on XCT effect on neurocognition.

CCT over 120 min, several reports have shown that there is a correlation between CCT and postoperative cerebral dysfunction. In our study there were 4 individuals who have cross clamp duration over 120 min and 3 of them a little bit more than 120 min (121, 123, 132). One of them 157 min. So, we could not have a conclusion about individuals who are over 120 min cross clamp duration.

Previous studies in the literature have shown that there is no significant correlation between CCT and neurocognitive function disorder under 120 min as in our study. Beside this, a strong relationship between CCT and neurocognitive function over 120 min has been reported in the literature.

**Table 1. Shows the descriptive feature distribution**

n=100	Min-max	Mean $\pm$ SD
Age (year)	39-77	$57.8 \pm 9.7$
Cross clamp time (min)	19-157	$62.6 \pm 27.8$

Min: Minimum, max: Maximum, SD: Standard deviation

**Table 2. Assessing the SMMSE relating to cross clamp time**

		Cross clamp time	
		r	p
SMMSE point	Pre-op	-0.117	0.246
	Post-op	-0.027	0.787
	Difference (preop-postop)	-0.160	0.111

r: Spearman correlation parameter, SMMSE: Standardized mini mental state examination

**Table 3. Assessing the results for gender**

	Men (n=82)	Women (n=18)	p
	Mean $\pm$ SD	Mean $\pm$ SD	
Age (year)	$57.6 \pm 9.6$	$58.8 \pm 10.5$	0.617 <sup>a</sup>
CCT (min)	$62.1 \pm 26.7$	$65.2 \pm 33.2$	0.98 <sup>b</sup>
Pre-op SMMSE	$29.1 \pm 0.83$	$29.4 \pm 0.62$	0.156 <sup>b</sup>
Post-op SMMSE	$29.4 \pm 0.85$	$29.3 \pm 0.77$	0.415 <sup>b</sup>

<sup>a</sup>Student's t-test, <sup>b</sup>Mann-Whitney U test, SD: Standard deviation, CCT: Cross clamp time, SMMSE: Standardized mini mental state examination



Although the current study is based on a small sample of participants, the findings suggest that CCT should be lower than 120 min in CABG not to a neurocognitive disorder. These results match with those observed in earlier studies.

### Study Limitations

A limitation of this study is that it is a single center study and the sample size over 120 min CCT is inadequate for the conclusion. An other limitation of this study is that some comorbidities such as tobacco use or diabetes mellitus are not evaluated.

A key strength of this work is being a prospective study and assessing the neurocognitive function face-to-face manner with a common reliable test.

Further study could assess the long-term effects of the cross clamp duration. Our study was limited to one week period starting on the day before surgery.

This experiment did not detect any evidence of CCT over 120 min.

The current study pointed out that there is no significant difference between young and elderly participants and women and men.

## CONCLUSION

The study confirmed that CCT under 120 min has no significant impact on neurocognitive function.

The principal theoretical implication of this study: CCT <120 min is a safety zone for neurocognitive function.

### Ethics

**Ethics Committee Approval:** Approved by the University of Health Sciences Turkey, İstanbul Dr. Siyami Ersek Thoracic Cardiovascular Surgery Training and Research Hospital institutional Ethics Committee (BŞH.FR.40, decision date: 11.02.2015).

**Informed Consent:** Written informed consent was obtained.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: E.A., M.E.E., B.K., C.U.K., Concept: E.A., M.E.E., B.K., C.U.K., Design: E.A., M.E.E., B.K., C.U.K., Data Collection or Processing: E.A., M.E.E., A.O., M.A.K., Analysis or Interpretation: E.A., M.E.E., A.O., M.A.K., Literature Search: E.A., M.E.E., A.O., M.A.K., Writing: E.A., M.E.E., A.O.

**Conflict of Interest:** No conflict of interest was declared by the

authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Clinical Features of Patients with Infective Endocarditis in Emergency Department

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## Abstract

**Objective:** Infective endocarditis (IE) is a rare but life-threatening multisystem disease that results from infection of the endocardial surface of the heart. IE manifests with varied and uncommon symptoms so it is a tricky situation for emergency physicians; our goal is to present the clinical features and course of IE patients in emergency department.

**Methods:** This study was conducted retrospective and descriptive study was between January 1, 2010 and December 31, 2019. Patients aged over 18 years and diagnosed with definite IE or possible IE according to the modified Duke criteria were enrolled in the study. We statistically analyse the difference between non-survivors and survivors groups for age, gender, symptoms, co-existing conditions, laboratory and imaging results and IE related complications and surgical intervention.

**Results:** Twenty-nine patients enrolled in the study 20 patients (69%) were admitted with definite IE, and 9 patients (31%) met just possible IE diagnosis according to modified Duke's criteria. Five (17%) patients died from IE and related complications. *Staphylococcus aureus* subspecies are the prominent agents in the blood culture results. Twenty five of patients (86%) had significant echocardiographic findings. Mitral and aortic valves the most affected parts of the endocardial surface in our study.

**Conclusion:** IE should be considered in patients with fever and predisposing heart conditions. IE related complications may change the course of the disease. Surgical intervention reduces the mortality rate so that it is beneficial for selected patients.

**Keywords:** Infective endocarditis, emergency department, *Staphylococcus aureus*, mortality

## INTRODUCTION

Infective endocarditis (IE) is an uncommon multisystem problem that results from infection of the endocardial surface of the heart (1). The term of "endocarditis" was originally used in the early 19<sup>th</sup> century. It is referred to the inflammatory processes in the endocardial tissue of the symptomatic patients after clinical anatomy based autopsy studies (2). Considering medical advances, IE has evolved and changed its patient profiles and clinical characteristics over the decades. At the present times prosthetic valve replacement, indwelling devices, hemodialysis, venous catheters, immunosuppression, and intravenous (IV) drug use have become the principal risk factors (3-5). IE is

an uncommon disease that diagnosing is quite difficult and complicated. Its annual incidence ranges from 3 to 7 per 100.000 person-years. Although relatively rare, it can cause significant morbidity and mortality if unrecognized and treated (4-6). The Gram-positive cocci such as the *Staphylococcus*, *Streptococcus*, and *Enterococcus* species are accounted for 80-90% of overall. *Staphylococcus aureus* is a leading cause of IE cases in many regions of the world (5-9). The modified Duke criteria were recommended for diagnostic classification. These criteria are based on clinical, echocardiographic and biological findings, as well as the results of blood cultures, serologies, and other imaging techniques (4,10). Echocardiography is the most



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**Received:** 18.06.2021

**Accepted:** 22.11.2021

**Cite this article as:** Çakmak F, Demirtakan T, Özkan S, Yıldız A, Biberöglü S, İpekci A, İkizceli İ. Clinical Features of Patients with Infective Endocarditis in Emergency Department. Eur Arch Med Res 2022;38(4):248-254

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important imaging such that transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE) for absolute diagnosis. Multislice computed tomography (CT), radiolabeled leukocyte scintigraphy or  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scanning, magnetic resonance imaging (MRI) are the auxiliary imaging techniques for demonstrating specific complications (7,11-14). Pathogen-specific recommendations for antibiotics are complex and are well summarized in recent guidelines. Optimal therapy of IE requires high dose IV bactericidal antibiotics for a prolonged period. Valvular surgery should be considered for the specific patient group (4,10,12).

William Osler said “Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties that in many cases are practically insurmountable.” while describing IE as “malignant endocarditis” (15). Because the serious chaos environment in the emergency room, an emergency physician should always be aware of recognizing IE among the relevant patient groups. Therefore, we are aiming to present the clinical features and course of IE patients in a tertiary-care university hospital emergency department (ED).

## METHODS

This descriptive retrospective single center study was conducted at the ED of a university hospital by scanning patients' data between January 1, 2010 and December 31, 2019. Patient data were obtained by scanning the hospital automation program (ISHOP) related diagnostic codes with acute and subacute endocarditis, and those were re-evaluated according to the modified Duke criteria and included in the study. Patients aged over 18 years and diagnosed with definite IE or possible IE according to the modified DUKE criteria were enrolled in the study. Patients who were re-diagnosed or re admitted in 6 months after their first episodes were included in the study as a different case. The Clinical Researches Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Ethical Board approved this study based on retrospective design by approval number 31887016-804.01-195972.

The data about the participants were obtained from the ISHOP system and the Ministry of Health Death Electronic Registration System. Age, gender, comorbid conditions (previous IE, congenital heart disease, valvular heart disease, malignancy, immunosuppressive conditions, and dialysis), predisposing factors (presence of catheter, IV drug use, dental procedure) were recorded for each patient. Symptoms at the first admission to the ED, fever, pulse, blood pressure, respiratory rate, oxygen saturation, Glasgow Coma score, and laboratory results were

evaluated as baseline variables. Transthoracic and TEE findings of all participants in the study were obtained and the ejection fraction and affected valve were recorded. Additionally, PET/CT and cardiac MRI were also used in patients with an indication. Microbiological data were obtained from blood culture results. In the clinical course, IE-related embolic events, acute renal failure, congestive heart failure, abscess and metastatic infections and surgical intervention were evaluated as complications and added to the study. Length of stay and in-hospital mortality are variables that determine the clinical outcome.

## Statistical Analysis

Data statistics were performed using IBM SPSS Statistics 21 for the Windows program. Descriptive results are given by mean and standard deviation for continuous variables. Categorical data are shown by the number of observations and frequency (n, %). The suitability of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Chi-square tests are used to compare categorical variables. Mann-Whitney U test was used to compare two groups.  $P < 0.005$  value was accepted as significant.

## RESULTS

Twenty-nine patients were included in the study who were detected with the specified diagnostic codes in computerized health record system. Twenty patients (69%) were admitted with definite IE, and 9 patients (31%) met just possible IE diagnosis according to modified Duke's criteria. Mortality was seen in 5 (17%) patients due to IE and related complications. The mean age of the patients was  $56.3 \pm 18.8$  years and it ranges between 19 and 89. 41% of the patients are women and there is no significant difference in gender between patients who died and survived. Acquired valvular disease was noted in 19 (66%) IE patients. In the following, immunosuppressive conditions (24%) and malignancy (21%) are other important risk factors. Non-specific symptoms like fever (76%), fatigue (69%), dyspnea (38%), palpitation (34%), and chest pain (17%) are reported as the initial complaints in ED. A cardiac murmur was the most common physical examination finding in our study. Mean body temperature and respiratory rate were significantly higher in non-survivors than in survivors (Table 1). There is no significant difference between non-survivors and survivors for laboratory results such as white blood count, platelet, C-reactive protein, total bilirubin, erythrocytes sedimentation rate and lactate levels (Table 1).

Twenty-one patients had significant blood culture results according to modified Duke's major criteria. *S. aureus* subspecies,

<b>Table 1. Initial characteristics of IE patients in emergency department</b>				
	<b>All patients n=29</b>	<b>Survivors n=24</b>	<b>Non-survivors n=5</b>	<b>p</b>
Age, mean $\pm$ SD (min-max)	56.3 $\pm$ 18.8 (19-89)	54.8 $\pm$ 19.4 (19-89)	63.6 $\pm$ 15.0 (48-82)	0.352
<b>Characteristics, n (%)</b>				
IE according to Duke' criteria	29	24 (83%)	5 (17%)	-
Definite	20 (69%)	16 (67%)	4 (80%)	
Possible	9 (31%)	8 (33%)	1 (20%)	
<b>Gender, n (%)</b>				
Male	17 (59%)	13 (54%)	4 (80%)	0.370
Female	12 (41%)	11 (46%)	1 (20%)	
<b>Comorbidities and risk factors, n (%)</b>				
Acquired valvular heart disease	19 (66%)	15 (63%)	4 (80%)	0.633
Immunosuppression	7 (24%)	5 (21%)	2 (40%)	
Malignity	6 (21%)	4 (16%)	2 (40%)	
Previous IE history	3 (10%)	3 (13%)	0 (0%)	
IV drug use	3 (10%)	3 (13%)	0 (0%)	
Presence of catheter	3 (10%)	1 (4%)	2 (40%)	
Hemodialysis	3 (10%)	1 (4%)	2 (40%)	
Dental procedure	3 (10%)	2 (8%)	1 (20%)	
Congenital heart disease	1 (3%)	1 (4%)	0 (0%)	
<b>Initial symptoms, n (%)</b>				
Fever	22 (76%)	18 (75%)	4 (80%)	1.000
Fatigue	20 (69%)	18 (90%)	2 (40%)	0.287
Dyspnea	11 (38%)	8 (33%)	3 (60%)	0.339
Palpitation	10 (34%)	8 (33%)	2 (40%)	0.339
Chest pain	5 (17%)	5 (21%)	0 (0%)	-
<b>Physical examination, n (%)</b>				
Murmur	23 (79%)	19 (79%)	4 (80%)	1.000
Purpura	5 (17%)	4 (17%)	1 (20%)	
Other signs	1 (4%)	0 (0%)	1 (20%)	
<b>Vital signs, mean <math>\pm</math> SD</b>				
Body temperature	37.8 $\pm$ 9.5	37.6 $\pm$ 8.8	38.8 $\pm$ 7.8	0.016
Systolic blood pressure	119.2 $\pm$ 18.6	118.4 $\pm$ 16.3	122.8 $\pm$ 29.4	0.758
Diastolic blood pressure	72.3 $\pm$ 10.4	71.2 $\pm$ 9.7	77.2 $\pm$ 13.3	0.352
Heart rate	98.2 $\pm$ 20.8	97.7 $\pm$ 21.3	100.6 $\pm$ 20.2	0.556
Oxygen saturation	95.4 $\pm$ 2.7	95.6 $\pm$ 2.9	94.4 $\pm$ 1.5	0.201
Respiratory rate	20.3 $\pm$ 2.8	19.8 $\pm$ 2.7	22.8 $\pm$ 2.3	0.037
GCS	14.7 $\pm$ 0.6	15 (0)	14.2 $\pm$ 1.3	0.382
<b>Laboratory results, mean <math>\pm</math> SD</b>				
White blood cells ( $\times 10^3/\text{mm}^3$ )	9.0 $\pm$ 3.7	9.2 $\pm$ 3.6	7.7 $\pm$ 5.2	0.594
Platelets ( $\times 10^3/\text{mm}^3$ )	2.0 $\pm$ 1.4	2.0 $\pm$ 1.3	2.0 $\pm$ 0.2	0.801
C-reactive protein	226.5 $\pm$ 52.9	224 $\pm$ 56.3	240.3 $\pm$ 21.9	0.222
Total bilirubin	2.1 $\pm$ 1.2	1.3 $\pm$ 1.0	1.5 $\pm$ 1.1	0.352
<b>Erythrocytes sedimentation rate, mean <math>\pm</math> SD</b>				
1 <sup>st</sup> hour	62.8 $\pm$ 27.8	62.3 $\pm$ 27.1	66.0 $\pm$ 39.3	0.663
2 <sup>nd</sup> hour	100.2 $\pm$ 33.2	102.1 $\pm$ 32.5	86.6 $\pm$ 17.6	0.606
Lactate	5.0 $\pm$ 1.9	5.7 $\pm$ 2.0	1.6 $\pm$ 0.6	0.900

IE: Infective endocarditis, GCS: Glasgow Coma score, SD: Standard deviation, IV: Intravenous, min: Minimum, max: Maximum

*Streptococci* and *Enterococci* were the prominent species in the blood culture results. Beside microbiological evidence, 25 of the patients (86%) showed significant echocardiographic findings as well. Mitral valve and aortic valves were the most affected parts of the endocardial surface in our study. In 8 patients (28%) echocardiographic evidence was detected on both mitral and aortic valve. Separately, mitral valve and aortic valves were affected in 6 (21%) and 5 (17%) patients, respectively. The right side of the heart was infected in 6 (20%) patients associated with tricuspid valve and implantable devices. All died patients (100%) had remarkable echocardiographic evidence; however, just 69% of survivors had significant findings on TEE or TTE examination (Table 2).

Considering the Duke's minor criteria; fever was recorded in 76% of patients and predisposing heart factors were seen in 59%.

Characteristics	All patients n=29	Survivors n=24	Non- survivors n=5	p
<b>Significant blood culture for IE</b>	21 (72%)	16 (67%)	5 (100%)	<b>0.016</b>
MSSA	9 (31%)	7 (29%)	2 (40%)	
MRSA	3 (10%)	2 (8.3%)	1 (20%)	
<i>Streptococci</i>	4 (14%)	3 (13%)	1 (20%)	
<i>Enterococci</i>	5 (17%)	4 (17%)	1 (20%)	
<i>Candida albicans</i>	1 (3%)	1 (4%)	0 (0%)	
Not detected	8 (28%)	8 (100%)	0 (0%)	<b>0.003</b>
<b>Significant ECHO findings for IE</b>	25 (86%)	20 (83%)	5 (100%)	
Mitral valve	6 (21%)	4 (17%)	2 (40%)	
Aortic valve	5 (17%)	4 (17%)	1 (20%)	
Tricuspid valve	3 (10%)	2 (8%)	1 (20%)	
Mitral + aortic valve	8 (28%)	7 (29%)	1 (20%)	
Implantable devices	3 (10%)	3 (13%)	0 (0%)	<b>1.000</b>
<b>PET/CT</b>	3 (10%)	3 (13%)	0 (0%)	
<b>Cardiac CT</b>	4 (14%)	3 (13%)	1 (20%)	<b>1.000</b>
<b>Predisposing heart conditions</b>	17 (59%)	14 (58%)	3 (60%)	
<b>Fever</b>	22 (76%)	18 (75%)	4(80%)	<b>1.000</b>
<b>Immunological signs</b>	1 (3%)	1 (4%)	0 (0%)	-
<b>Vascular phenomena</b>	5 (17%)	4 (17%)	1 (20%)	-
<b>Other microbiological evidences</b>	6 (20%)	6 (21%)	0 (0%)	-

IE: Infective endocarditis, MSSA: Methicillin-susceptible *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*, ECHO: Echocardiography, PET/CT: Positron emission tomography/computed tomography

Minor microbiological findings that are inadequate for Duke's major criteria (20%), vascular phenomena (17%), immunological signs (3%) were the other criteria that our patients had met for IE (Table 2).

IE related complications such as embolic events, akut kidney injury, congestive heart failure, metastatic abscess and spondylitis were observed in 14 (48%) patients. Gentamicin added cefazolin or amoxicillin and gentamicin added vancomycin combinations were the most preferred antibiotic regimens in our study. Median day of their antibiotherapy duration was the same, 28 days for both. Thirteen patients had undergone surgery due to IE related severe valve failure and 12 of those were survived after surgery. The mean length of stay in the hospital for all patients was  $30.5 \pm 14.7$  days. Survived patients stayed significantly longer than non-survivals, and the mean length of hospital stay of non-survivors and survivors was  $34.1 \pm 13.2$  and  $13.4 \pm 8.5$  days, respectively (Table 3). In univariable regression analysis, body temperature had a significant odds ratio for in-hospital mortality ( $p=0.040$ , 95% confidence interval, odds ratio: 1.120) (Table 4).

## DISCUSSION

Clinical presentation of the IE is polymorphic, variable and symptoms are non-specific (13). Peripheral and more typical signs, such as Osler nodes, Janeway lesions, Roth spots, are quite rare and seen at the late stage in subacute forms (15). Difficulties and challenges of the IE diagnostic results in delaying the rapid antibiotic therapy. This study may lead the emergency room doctors to be aware of the potetinal IE patients.

Totally 411.716 over 18 years old patients were admitted to the ED in ten years. Ten-years-incidence of our department is 7-8/100,000 and this incidence rate is a bit more than ESC and AHA guidelines (4-6). Male gender was dominant in our study population (59%). Mean age of the patients was 56.3 years and interestingly, Leblebicioglu et al. (16) reported the mean age of the IE patients in Turkey as 45.2 years in 2006. In this point, our results are similar to those of Northern Europe and France sourced IE reviews' (17,18). A growing number of the elderly population and decreasing of the pediatric rheumatic valve disease incidence in Turkey can be the reasons for this transition to the elder age group of the IE patients (19,20).

Predisposing heart diseases are a prominent risk factors in this presented study and as well as recent other studies. IE was previously more often related to rheumatic heart disease in younger patients, but it is now is more frequent in older patients, and the number of associated risk factors is increasing. Malignity, immunodeficiency diseases and related treatments



**Table 3. Complication, surgery, antibiotherapy and length of hospital stay rates of patients**

	All patients n=29	Survivors n=24	Non-survivors n=5	p
Complications	14 (48%)	12 (50%)	2 (40%)	-
Embolic events	5 (17%)	4 (17%)	1 (20%)	-
Acute kidney injury	6 (21%)	5 (21%)	1 (20%)	-
Congestive heart failure	1 (3%)	1 (4%)	0 (0%)	-
Abcess	1 (3%)	1 (4%)	0 (0%)	-
Spondylitis	1 (3%)	1 (4%)	0 (0%)	-
<b>Antibiotic regimen n (%)</b>				
Cefazolin or amoxicillin + gentamicin	10 (34%)	9 (38%)	1 (20%)	-
Vancomycin + gentamicin	10 (34%)	9 (38%)	1 (20%)	-
Daptomysin, only	6 (20%)	4 (16%)	2 (40%)	-
Daptomysin + rifampin	1 (3%)	1 (4%)	0 (0%)	-
Daptomysin + PIP + TAZO	1 (3%)	0 (0%)	1 (20%)	-
Vancomycin, only	1 (3%)	1 (4%)	0 (0%)	-
<b>Antibiotherapy duration, day (median, IQR)</b>				
Cefazolin or amoxicillin + gentamicin	28.0 (19.0)	28.0 (19.0)	2.0	-
Vancomycin + gentamicin	28.0 (25.0)	28.0 (25.0)	12.0	-
Daptomysin only	28.0 (12.5)	28.0 (12.75)	7.5	-
Daptomysin + rifampin	42.0	42.0	-	-
Daptomysin + PIP + TAZO	18.0	-	18.0	-
Vancomycin, only	21.0	21.0	-	-
<b>Surgery</b>	13 (45%)	12 (50%)	1 (20%)	-
<b>Length of hospital stay</b>	30.5±14.7	34.1±13.2	13.4±8.5	<b>0.002</b>

PIP + TAZO: Piperacillin + tazobactam, IQR: Interquartile range

**Table 4. Univariate and multivariate regression analyses for mortality**

Risk factors	Univariate analyse		Multivariate analyse	
	OR (95% CI)	p value	OR (95% CI)	p value
Body temperature	1.120	0.040	-	0.210
Respiratory rate	-	0.054	-	-
Significant blood culture	-	0.999	-	-
Significant ECHO findings	-	0.999	-	-
Length o stay in hospital	0.812	0.032	-	0.426

CI: Confidence interval, OR: Odds ratio, ECHO: Echocardiography

make the patients vulnerable to persistent infections. Therefore, cancer and immunodeficiency are the other major causes of IE (4-6,21). Presence of catheter and routine hemodialysis and the increasing proportion of the IE etiology. Especially central line associated bacteremia in chronic renal disease patients mostly transforms to the infectious endocardial surface (17,18). Asgeirsson et al. (17) revealed that IV drug using is the most

common specific underlying conditions in *S. aureus* associated IE. Only three patients have an IV drug using history however IV drug use is another growing risk factor for IE (21,22).

Most common symptom and physical examination findings are fever and heart murmur just as reported in previous studies (4,6,22). Other clinical features are fatigue, dyspnea and palpitation in the first sight in the ED. According to our results, measured body temperature and breath rate are significantly higher in deads. Just inflammation markers, which are C-reactive proteins and erythrocyte sedimentation rate excessively higher than the cut-off value and other considered laboratory findings do not affect the mortality. Our results are in coherent with Şimşek-Yavuz et al.'s (23) that they reported no significant difference in white blood cell counts, creatinine, C-reactive protein, and erythrocyte sedimentation rate between deads and survivors however only blood thrombocyte counts were significantly higher in dead IE patients.

*Staphylococcus aureus* bacteremia (SAB) incidence has been increasing because of older population age, hemodialysis, IV drug using and consecutive interventional process. For those

who with SAB face a risk of IE whether immunocompromised or not. Current guidelines express that *S. aureus* is the most frequent microbiological cause of IE. Furthermore, *S. aureus* caused IE has a worse prognosis than other IE forms associated microorganisms (17,24). In this presented study, *S. aureus* was reproduced in 41% % of the significant blood cultures, which is higher than Şimşek-Yavuz et al. (23) and Vahabi et al.'s (22) findings. We did not detect any coagulase-negative *Staphylococcus* but in overall 68% of the significant blood culture for IE was Gram-positive coccus, which includes *Streptococci* and *Enterococci* as well. 28% of the cases considered as culture-negative endocarditis who diagnosed with echocardiographic evidence and other minor criteria of Duke. Fungal IE prevalence changes between 1 and 10 % of all IE cases. *Candida* spp. are isolated in 53-68% of fungal endocarditis with *C. albicans* is the most common (25). We observed that one surviving patient with implantable cardioverter-defibrillator had *C. albicans* associated IE. Brucella endocarditis is rare but Brucellosis is endemic in the Mediterranean and the Middle East (26). Brucella endocarditis was not reported in this study. This might be the reason for this result that the decreased consumption of unpasteurized milk in city centers in Turkey.

Transeosophageal and TTE both were performed for each patient in our study and diagnostic evidence for IE was found in 86%. <sup>18</sup>F-FDG PET/CT was performed for 3 (10%) patients. A total of 4 (13%) underwent contrasted thorax CT to detect IE complications such as metastatic abscesses and rule out pulmonary embolism for symptomatic individuals. According to previous studies, those imaging technics reveals that mitral and aortic valves, either separately or both are mostly affected part of heart (4,10). However, tricuspid valve and implantable device infection, which means the right side endocarditis rate is totally 20% in this presented study and approximately as same as Zencirkiran Agus et al.'s (27) results.

Recent studies show that the mortality rate for IE is approximately 20% within the first 30 days, though exact rates vary between population-based studies (28). According to our study, 5 (17%) patients died from IE and related complications. Embolic events had the highest frequency among the other complications, such as acute kidney injury, CCF, metastatic abscesses and spondylitis. Embolic complications more often affected the neurologic system such that in some cases we diagnosed IE through cerebrovascular embolism-related symptoms. Multiple studies have expressed the benefit of appropriate timing for surgery to decrease morbidity and mortality in selected patients (28). Our findings also support previous studies that overall 13 patients (45%) in this study underwent valve surgery due of severe valve regurgitation related IE and only one patient died after surgical

intervention. Average duration in the hospital of the patients in this study is  $30.5 \pm 14.7$  days that which is little shorter than Şimşek-Yavuz et al.'s (23) results ( $36.59 \pm 22.79$  days), nevertheless survivors stayed significantly longer than died patients in the hospital in both studies.

### Study Limitations

Infected endocarditis research in the literature were conducted as large multicenter studies. We designed this study with patients who were diagnosed in the ED of a single center; therefore, the study population remains smaller than other similar studies in the literature.

## CONCLUSION

IE may occur in all age groups and manifest with varied symptoms. Emergency physicians should consider IE in patients with fever and predispose heart conditions. *S. aureus* subspecies have the highest frequency, mitral and aortic valves either separately or both are mostly affected part of the heart. IE related complications may change the course of the disease. Surgical intervention reduces the mortality rate so that it is beneficial for selected patients.

### Ethics

**Ethics Committee Approval:** The Clinical Researches Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Ethical Board approved this study based on retrospective design by approval number 31887016-804.01-195972.

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: F.Ç., T.D., S.Ö., A.Y., S.B., A.İ., İ.İ., Design: F.Ç., T.D., S.Ö., A.Y., İ.İ., Data Collection or Processing: F.Ç., T.D., S.B., A.İ., İ.İ., Analysis or Interpretation: F.Ç., T.D., S.Ö., A.İ., Literature Search: F.Ç., T.D., S.Ö., A.Y., S.B., A.İ., İ.İ., Writing: F.Ç., T.D., S.Ö., A.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Do Dermatological Diseases Cause Disability? A Single Tertiary Center Experience

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## Abstract

**Objective:** Chronic skin diseases can negatively affect the quality of life. They may cause impairment of work productivity and have a socio-economical burden. In this study, we evaluated patients who applied to our hospital for the determination of disability due to chronic skin diseases.

**Methods:** We retrospectively evaluated the patients who were given a disability rate by our department between 2008 and 2018. The demographic features of the patients, diagnosis of the skin disease, involved areas of the body and accompanying comorbidities were recorded. Skin diseases were classified and rates of disabilities were determined according to the Ministry of Family, Labor and Social Services and the Ministry of Health's disability assessment scale for adults.

**Results:** A total of 137 patients were included in the study. Eighty-two (59.8%) of the patients were male and 55 (40.1%) were female. The mean rate of disability due to skin diseases was  $11.31 \pm 10.91$ . The mean rate of disability was 12.0 for male patients and 10.2 for female patients. The most common diseases causing disability were inflammatory skin diseases (22.6%), skin manifestations of autoimmune and systemic skin diseases (18.9%), skin tumors (16.7%) and eczema (11.6%). Psoriasis vulgaris is the most common (96.6%) inflammatory skin disease. Of the skin manifestations of autoimmune and systemic skin diseases, Behçet's disease (34.6%) accounted for most patients, while autoimmune bullous diseases had the highest rate of disability. Malignant melanoma had the highest disability rates among skin tumors. Among the eczema group, patients with contact dermatitis (62.5%) had the highest rate of disability. Patients with genetic skin diseases, such as ichthyosis, epidermolysis bullosa and lipoid proteinosis, had the highest rate of disability overall.

**Conclusion:** Chronic skin diseases may cause disability as well as a decrease in quality of life. Patients with chronic skin disease should be evaluated with their psychological and occupational aspects.

**Keywords:** Skin disease, disability, quality of life

## INTRODUCTION

Skin diseases are very common and can affect individuals of all ages worldwide. Globally, skin conditions are reported as the fourth leading cause of all human diseases. Although many of the skin diseases are not life-threatening, they may result in a significant burden on the quality of life, including psychosocial and economic impacts. The presence of skin diseases in visible areas of the body often leads to decreased self-confidence and social withdrawal. Symptoms such as pruritus, pain and fatigue

due to the chronic dermatoses can also decrease the quality of life of the patients (1-4).

Occupational dermatoses also have a significant economic burden to the healthcare providers. Occupational dermatoses cause a decrease in work productivity and loss of work occasionally. Both the physical disability and cost of treatment contribute to the economic burden on society (4,5).

In this study, we evaluated patients who applied to our hospital for assessing disability due to chronic skin diseases.



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**Received:** 07.07.2021  
**Accepted:** 28.11.2021

**Cite this article as:** Ağaoğlu E, Kaya Erdoğan H, Acer E, Saraçoğlu ZN. Do Dermatological Diseases Cause Disability? A Single Tertiary Center Experience. Eur Arch Med Res 2022;38(4):255-260

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European Archives of Medical Research published by Galenos Publishing House.

## METHODS

We included patients with any skin disease who were admitted for the determination of disability due to chronic skin diseases to the health board of our hospital between 2008 and 2018. Patient files were retrospectively evaluated. Demographic features (age and gender) of the patients, the diagnoses of the skin diseases, involved areas of the body, accompanying comorbidities, and disability rates given by our department were recorded.

Skin diseases were classified according to the Ministry of Family, Labor and Social Services and Ministry of Health's disability assessment scale for adults. Psoriasis vulgaris (PV) and lichen planus were evaluated in the inflammatory skin disease group; whereas Behçet's disease (BD), connective tissue diseases vasculitis, autoimmune bullous diseases, pyoderma gangrenosum, and chronic graft-versus-host disease were included in the skin manifestations of immune and autoimmune systemic diseases. Hypertrophic scars and hemangiomas were classified as benign skin tumors, whereas malignant melanoma, and squamous cell carcinoma were classified as malignant skin tumors. Contact dermatitis, atopic and seborrheic dermatitis were grouped in the eczema group (6).

The study protocol was approved by the Eskisehir Osmangazi University Faculty of Medicine, Ethics Committee (approval number: 310, date: 25.12.2018).

### Statistical Analysis

The SPSS 22.0 software was used for data analysis. Continuous quantitative data were expressed as n, mean, and standard deviation, and qualitative data were expressed as n and median.

## RESULTS

A total of 137 patients were included in the study. Eighty-two (59.8%) of the patients were male and 55 (40.1%) were female. The mean age of the patients was  $40.75 \pm 14.06$  (range: 6-71). The mean rate of disability due to the skin diseases was  $11.31 \pm 10.91$ . The mean rate of disability was 12% for male patients and 10.2% for female patients. Of the total percentage disability, the most common diseases were inflammatory skin diseases (22.6%), skin manifestations of autoimmune, and systemic skin diseases (18.9%), skin tumors (16.7%), and eczema (11.6%). Thirty (96.6%) of 31 patients with inflammatory skin disease were PV. The most common comorbidities accompanying PV were psoriatic arthritis (20%) and psychiatric disorders (16.6%). Persistent depressive disorder (dysthymia) was recorded as the most common (50.0%) psychiatric disorder in psoriasis patients.

In the immune and autoimmune skin disease groups, BD (34.6%) constituted most patients, while the highest rate of disability

was given to the autoimmune bullous diseases. Eye involvement was noted in 5 (55.5%) patients with BD. While 4 (44.4%) patients with BD had oral ulcers, 3 (33.3%) had both oral and genital ulcers. The most common comorbidities accompanying patients with BD were adjustment disorder (44.4%) and Crohn's disease (33.3%). Among the connective tissue diseases, 4 (66.6%) patients were cutaneous lupus erythematosus, while dermatomyositis and antiphospholipid antibody syndrome were recorded, each in one patient. Adjustment disorder was noted in 2 (50.0%) patients with cutaneous lupus erythematosus. Of the autoimmune bullous diseases, all the patients were pemphigus vulgaris. Malignant skin neoplasms (6 patients) had the highest disability rates among skin tumors. Four (66.6%) patients had malignant melanoma and two (33.3%) patients had squamous cell carcinoma. Among the eczema group, patients with contact dermatitis (62.5%) accounted for the majority of the patients (Table 1). Six (60.0%) patients with contact dermatitis had hand involvement.

Patients with genetic skin diseases such as ichthyosis, epidermolysis bullosa (EB) and lipoid proteinosis had the highest rate of disability overall. After those with genetic skin diseases, patients with mycosis fungoides (MF) had the highest rate of disability in the less common disease group (Table 2).

## DISCUSSION

Several studies have focused on the clinical outcomes of dermatological diseases, however the economic and psychosocial aspects of the chronic dermatoses are poorly described. The direct costs of skin diseases are defined as medical care or hospitalization, while indirect costs for the society comprise sick leave, loss of productivity at work, impairment and unemployment (7-9). Patients with chronic dermatoses often experience a reduced working capacity due to the physical disability (4).

Psoriasis is a common chronic skin disease characterized by itching, scaling and disfiguring skin changes (10). There are many studies have revealed that psoriasis negatively affects both the quality of life and work productivity (11-14). In a study of 369 patients with severe psoriasis, approximately 60% of employed patients declared that they had reduced working capacity, and 34% of the patients who were not working indicated that the reason was psoriasis (11). Chan et al. (12) reported that 38% of the patients with psoriasis have difficulty finding a job, whereas 19% of the patients had impairment at work. Additionally, it was shown that the annual income from employment had decreased in patients with psoriasis compared with the normal population



Disease groups (the most common)		Number of patients n (%)	Mean rate of disability	
Inflammatory skin diseases	Psoriasis vulgaris	30 (96.7%)	12.5	
	Lichen planus	1 (3.3%)	5.0	
Skin manifestations of immune and autoimmune systemic diseases	Behçet's disease	9 (34.6%)	15.0	
	Connective tissue diseases	6 (23.0%)	13.3	
	Vasculitis	5 (21.7%)	8.0	
	Autoimmune bullous diseases (Pemphigus)	3 (11.5%)	30.0	
	Pyoderma gangrenosum	2 (7.6%)	5.0	
	Chronic GVHD	1 (4.3%)	10.0	
Skin tumors	Benign skin neoplasms	Hypertrophic scar	12 (52.1%)	5.4
		Hemangioma	5 (21.7%)	8.0
	Malignant skin neoplasms	Malignant melanoma	4 (17.3%)	15.0
		Squamous cell carcinoma	2 (8.6%)	10.0
Eczematous dermatitis	Contact dermatitis	10 (62.5%)	7.0	
	Atopic dermatitis	3 (18.7%)	3.3	
	Seborrheic dermatitis	3 (18.7%)	1.6	

GVHD: Graft-versus-host disease

Disease groups (the less common)		Number of patients n (%)	Mean rate of disability
Genetically transmitted skin diseases	Ichthyosis	3 (37.5%)	40.0
	Keratoderma	2 (25.0%)	17.5
	Epidermolysis bullosa	1 (12.5%)	40.0
	Neurofibromatosis	1 (12.5%)	10.0
	Lipoid proteinosis	1 (12.5%)	30.0
Sebaceous, eccrine and apocrine gland diseases	Acne vulgaris	3 (42.8%)	11.6
	Hidradenitis suppurativa	2 (28.5%)	15.0
	Rosacea	1 (14.2%)	5.0
	Hyperhidrosis	1 (14.2%)	10.0
Pigmentation disorders	Vitiligo	5 (100.0%)	12.0
Skin diseases with psychiatric etiology	Prurigo	2 (100.0%)	2.5
Skin diseases associated with hair follicle	Alopecia universalis	2 (100.0%)	10.0
Skin diseases due to microbial agents	Cutaneous tuberculosis	2 (100.0%)	2.5
Cutaneous leukemia and lymphomas	Mycosis fungoides	2 (100.0%)	25.0
Other skin diseases		13 (9.4%)	5.3

(14). In our study, most patients who applied for assessing disability were diagnosed with PV (21.8%).

It is also well known that psychosocial impacts of psoriasis decrease the quality of life. Patients with psoriasis often suffer from feelings of embarrassment, low self-esteem and fear of stigmatization. Accompanying psoriatic arthritis also increase the impairment and the functional impairment constitutes a significant burden on patients' lives. Patients with psoriatic

arthritis often experience chronic pain, fatigue and functional limitations, which may predispose to psychiatric disorders (15). Many studies are revealed that patients with psoriasis are more susceptible to psychiatric disorders such as depression, anxiety and adjustment disorders (4, 10, 16, 17). In our study, we detected psoriatic arthritis (20%) and psychiatric disorders (16.6%) as the most common comorbidities in psoriasis patients. Additionally, persistent depressive disorder (dysthymia) was the most frequent psychiatric disorder in our psoriasis patients.

In our study, BD constituted most patients in the immune and autoimmune skin disease groups. BD is a chronic, inflammatory disorder characterized by mucocutaneous ulcers and the multisystemic involvement of ocular, musculoskeletal, vascular, gastrointestinal, and central nervous systems. In BD, recurrent painful mucocutaneous ulcers, and arthritis limit the daily life, however ocular, vascular, and neurological involvements increase morbidity and mortality (18). Epidemiological studies have shown that Turkey has the highest prevalence rate of BD in the world (19,20). Sut et al. (20) evaluated the direct and indirect costs of the BD and reported that indirect costs accounted for 32% of the total cost. Additionally, lost workdays were noted in 51 (43%) of the patients and those with ocular, vascular, neurological involvement had the highest rate of workday loss. Mumcu et al. (21) had reported that the impairment of daily activities was observed more prominently in patients with musculoskeletal involvement, while ocular involvement was associated with decreased working hours. In our study, ocular disease was the most common systemic involvement in BD who applied for assessing disability.

Autoimmune bullous dermatoses are a group of disorders that affect the skin and mucous membranes. It is well documented that this group of diseases generally causes great impairment on quality of life. Painful mucocutaneous blisters and erosions lead to productivity loss of the patients (22,23). Brodzky et al. (24) emphasized that pemphigus patients generally experience a temporary or permanent decrease in working ability. In another study, Heelan et al. (22) reported that approximately 50% of the patients with autoimmune bullous dermatoses were unemployed. In our study, in the immune and autoimmune skin disease group, patients with pemphigus had a higher rate of disability compared with the other diseases.

Recent studies have shown that the annual incidence of malignant skin tumors, including malignant melanoma and non-melanoma skin cancers continue to increase. Given the loss of productivity, sick leave and early retirement due to skin cancers, it remains a significant economic burden to society (25,26). Most of the cases of melanoma are diagnosed at a younger age compared to with non-melanoma skin cancers and as the survival rates are increasing due to the early detection. This may lead to an increase in some challenges, such as work disability, changing jobs and psychosocial problems in younger population (27,28). In our study, malignant skin tumors had higher disability rates compared to the benign skin neoplasms. Additionally, patients with malignant melanoma had higher disability rates than patients with squamous cell carcinoma.

The personal and social outcomes of occupational contact dermatitis are work-related disability, reduced quality of life, increased healthcare costs and sometimes job change. Hand eczema constitutes approximately 80% of the occupational contact dermatitis (29). In a study by Meding et al. (30), they found that construction workers had a higher risk of disability pension due to eczema. In the long term follow up study of occupational hand eczema patients, it was reported that 34% of the patients had changed their occupation, whereas 25% of the patients had experienced unemployment or early retirement (31). Although the occupations of the patients could not be evaluated in our study, hand eczema was found the most common (60%) involvement in eczematous dermatitis patients who applied for a disability rate.

As many of the genodermatose persist throughout life, they have a substantial physical and socio-economical burden both on patient and on their families. It is well documented that genetic skin diseases such as EB and ichthyosis negatively affect the quality of life (32-35). Tabolli et al. (32) showed that the physical disability in EB causes more impairment than other dermatological diseases. Additionally, it has been shown that absenteeism in the workplace and daily time for skin care has a significant burden on the ichthyosis patients' lives (33). Our study also showed that patients with EB and ichthyosis had the highest rate of disability.

MF is the most common form of cutaneous T-cell lymphomas. Even for patients in early stages, the disease may directly affect the quality of life. Patients with MF often experience limitations in daily activities, disturbed body perception, sleep disturbances and psychosocial stress (36-38). In a study by Demierre et al. (37), they reported that 94% of the patients with cutaneous T-cell lymphoma were worried about their disease and 55% of the patients declared that the disease interferes with their job capability, which resulted in missed work days. The chronic course of the disease constitute also a substantial financial burden for both patients and societies. Although we had a small number of patients with MF in our study, the disability rates of the patients were found to be high.

### Study Limitations

To the best of our knowledge, this is the first study evaluating the disability related to dermatological diseases in our country. The limitations of our study are being a retrospective design and the small number of patients who had been admitted for assessing disability rate to our hospital.

## CONCLUSION

Our study demonstrates that chronic skin diseases may cause disability and have a socio-economical burden. Since the psychological comorbidities often accompany skin diseases, the burden of the skin diseases may increase indirectly. Therefore, chronic skin diseases should be evaluated for their economic and psychological consequences and their physical outcomes.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Eskisehir Osmangazi University Faculty of Medicine, Ethics Committee (approval number: 310, date: 25.12.2018).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: E.A., H.K.E., E.Ac., Z.N.S., Design: E.A., H.K.E., E.Ac., Z.N.S., Data Collection or Processing: E.A., H.K.E., E.Ac., Analysis or Interpretation: E.A., H.K.E., E.A., Literature Search: E.A., H.K.E., E.Ac., Writing: E.A., H.K.E., E.Ac., Z.N.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Quadriceps Muscle Atrophy in Patients with Varus Gonarthrosis

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## Abstract

**Objective:** This study aimed to investigate which section of the quadriceps muscle has more evident muscle atrophy, in knees with gonarthrosis and genu varum.

**Methods:** In patients operated on because of gonarthrosis and varus alignment, intraoperative muscle biopsies are taken from the vastus lateralis (VL), vastus medialis (VM), and vastus intermedius (VI). The materials obtained were evaluated for connective tissue and fatty tissue and the ratio of atrophic muscle cells. The statistical evaluation is used to determine the relationship between atrophy and the varus angle.

**Results:** The mean varus angle is 11.7°. The results showed that the amounts of connective tissue in the VM muscle was significantly greater than in the VL and VI muscles ( $p=0.018$ ). Additionally, no difference is determined between VM, VI, and VL with respect to the ratio of atrophic muscle cells to total muscle cells. The ratio of fatty tissue in the VL muscle was found to be statistically significantly greater in females than in males ( $p<0.05$ ). The connective tissue was generally determined at a significantly higher rate in the VM muscle than in the VL and VI muscles.

**Conclusion:** With an increase in the varus angle of the knee, atrophy is seen to increase in the VM and VI muscles, and is more evident than atrophy in the VL muscle. Therefore, strengthening exercises directed at the VM for patients varus knees would be useful in the prevention of gonarthrosis.

**Keywords:** Gonarthrosis, atrophy, quadriceps weakness, knee

## INTRODUCTION

The presence of osteoarthritis in the knee constitutes a significant morbidity. Several factors impact the development of osteoarthritis, but the etiology is not yet been fully understood. Knee alignment is seen as a factor affecting osteoarthritis development. The natural normal knee joint alignment is 2°-3° of varus compared with the mechanical axis. Changes in knee alignment cause changes in lateral and medial weight-bearing (1,2).

In knees with normal alignment, 60%-80% of compressive loads passing from the knee pass immediately medial of the midline. In a varus knee, more of the load is transferred from the inner compartment. The adduction moment forces the knee into varus

and therefore causes compression in the medial compartment while walking because the grand reaction force vector passes from the medial of the knee joint (2). A greater adduction moment causes greater loading in the medial compartment. Sufficient quadriceps strength in healthy knees has a protective effect against the development of osteoarthritis.

The function of the muscles around the knee is to create movement, absorb loads, and provide dynamic stability of the joint (3). The weakness of the quadriceps muscle increases the load on the knee joint, causing pain and function loss in patients with osteoarthritis in the knee joint. There is up to 40% more weakness in the quadriceps muscle of patients with osteoarthritis compared with healthy individuals (4). A reduction in proprioception or sensory innervation of the knee joint with



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**Cite this article as:** Çınar İ, Aytekin K, Esenyele D, Esenyele CZ. Quadriceps Muscle Atrophy in Patients with Varus Gonarthrosis. Eur Arch Med Res 2022;38(4):261-267

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 24.08.2021

**Accepted:** 07.12.2021



advancing age causes an imbalance in the activity of the muscles stabilizing the joint, and this plays a role in the development of osteoarthritis (2). Structural changes in the muscles added to this imbalance in muscle function can inhibit the protective effect of the muscle system and thus contribute to the development of osteoarthritis (2). Muscle weakness is a significant additional risk factor in patients susceptible to the development and progression of knee osteoarthritis, particularly those with a misalignment of the lower extremity.

This study determines the presence of atrophy by histopathological examination of the quadriceps muscle and investigate the relationship with the varus angle and which section of the quadriceps muscle affected the most in patients with varus knee who have undergone surgery for gonarthrosis.

## METHODS

Approval for the study was obtained from the Giresun University Faculty of Medicine Local Research Ethics Committee (decision date: 21.06.2017, number of decisions: 8). Informed written consent was obtained from all patients.

The study included 32 patients who applied with total knee prosthesis for the diagnosis of primary gonarthrosis. All the patients who presented with complaints of severe knee pain were aged >50 years, had primary gonarthrosis and genu varum, and agreed to participate in the study.

The overall anatomic tibiofemoral angle was measured on standard length, standing anteroposterior knee radiographs measuring 14×17 in. The patients included in the study were diagnosed with grade 4 osteoarthritis according to the Kellgren-Lawrence classification on the semi-flexed radiographs and underwent surgical intervention (5).

Patients were excluded from the study if they had valgus knee alignment, inability to walk, any neurological problems, alcohol dependence, arthritis in the hip or knee, gonarthrosis that developed secondary to trauma, infection or inflammatory disease, a history of fracture to the same lower extremity, a history of surgery to the lower extremities, limb length discrepancy, hip dysplasia, diabetes mellitus, loss of muscle strength, Lasegue and reverse Lasegue positivity, or any neurological disease.

## Biopsy

Surgery was performed in all patients using an anterior midline incision and medial parapatellar arthrotomy. From the proximal of the skin incision, the muscle fibers of the vastus lateralis

(VL), vastus intermedius (VI), and vastus medialis (VM) obliquus are reached. Muscle fiber biopsies, 1×0.5 cm in size, were obtained from all patients at approximately 1 cm proximal to the musculotendinous junction.

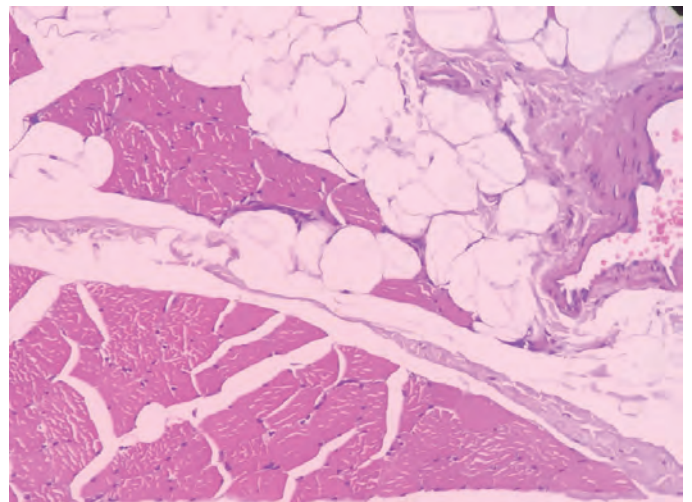
## Histopathological Evaluation

The pieces of muscle tissue obtained were fixed in 10% buffered formalin, then embedded in paraffin blocks in a manner that allows us to take sections both horizontally and transversely. Slices of 4 µm thickness were cut with a microtome from the paraffin blocks, then stained with hematoxylin and eosin (HE). The HE-stained specimens were evaluated under a light microscope using a pathology specialist (IC) and the results were recorded.

The evaluation criteria were as follows:

- 1- The presence and amount of fatty tissue within the muscle tissue (Figure 1),
- 2 - The presence and amount of connective tissue within the muscle tissue (Figure 2),
- 3- Ratio of atrophic muscle fibers to all muscle fibers (evaluated in 3 magnification areas).

No histomorphological atrophic muscle scoring system can be found in the literature. Therefore, for this study, reference was taken from the radiological classification of rotator cuff muscle fat degeneration of Goutallier et al. (6), and a scoring system was formed for the histomorphological evaluation of the presence of fatty tissue and fibrosis. Thus, the presence of fatty tissue and fibrosis within muscle tissue were evaluated separately and scored as follows:



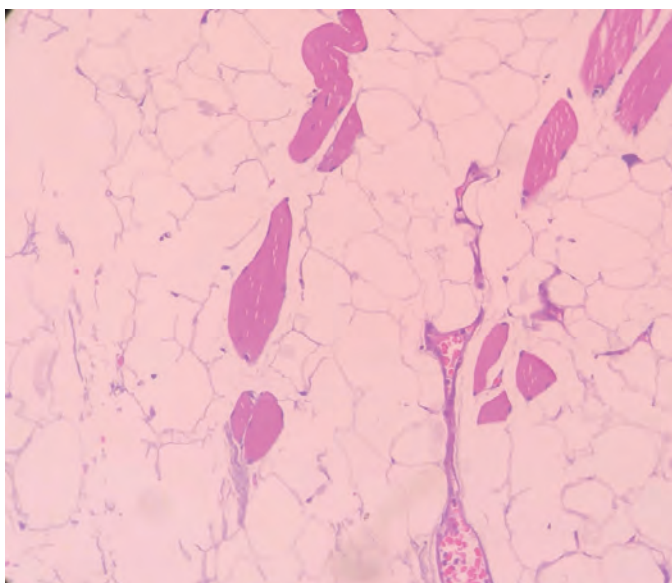
**Figure 1.** Atrophic muscle tissue with increased fat and connective tissue (hematoxylin and eosin stain, 10x100)

- Score 0: Normal muscle structure,
- Score 1: Occasional fatty or connective tissue,
- Score 2: <50% fatty tissue or fibrosis,
- Score 3: 50% fatty tissue or fibrosis,
- Score 4: >50% fatty tissue or fibrosis.

The ratio was determined in each specimen by counting the total muscle fibers and number of atrophic muscle fibers under 3 separate magnification areas (the number of atrophic muscle fibers/the total number of muscle fibers). The section in which atrophy was observed to be most intense, the ratio was determined in each specimen.

**Statistical Analysis**

Data obtained in the study were analyzed statistically using SPSS 22.0 software. Descriptive statistics of the data were stated as mean ± standard deviation, median, minimum and maximum values, number (n) and percentage (%). The conformity of the data to a normal distribution was assessed with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the evaluation of quantitative data. In the evaluation of dependent qualitative data, the Cochran's c-test and the McNemar test were used, and in the analysis of dependent quantitative data, the Friedman test was used. The chi-square test was applied in the analysis of dependent qualitative data and when chi-square test conditions were not met, the Fischer's exact test was applied. In the determination of correlations, Spearman's correlation analysis was performed. A value of p<0.05 was set as statistically significant.



**Figure 2.** Atrophic muscle fibers in adipose tissue (hematoxylin and eosin stain, 10x100)

**RESULTS**

The evaluation was made of 32 patients comprising 5 (15.6%) males and 27 (84.4%) females with a mean age of 67.62 years (range, 53-77 years). Surgery was performed on the right knee in 15 (46.9%) patients and the left knee in 17 (53.1%). All the patients were determined by grade 4 gonarthrosis according to the Kellgren-Lawrence classification (25). The mean lower extremity alignment of all patients was determined as 11.666° (range, 4°-22°) genu varum.

**Atrophic Muscle Cell Ratio**

No significant difference was determined in the atrophic muscle cell ratio of the VL, VM ve VI (p>0.05) (Table 1). No significant correlation was observed between age and gender and the atrophic muscle cell ratios of the VM, VL, and VI muscles (p>0.05). No significant correlation was determined between the varus angle and the atrophic muscle cell ratio of the VL muscle. A statistically significant positive correlation was determined between the varus angle and the atrophic muscle cell ratio of the VM and VI muscles (p<0.05) (Table 2).

**Fatty Tissue**

No significant difference was observed between the fatty tissue results of the VM, VL, and VI muscles (p>0.05). Fatty tissue in the VL muscle was determined at a statistically significantly higher rate in females (p<0.05). No significant difference was observed between males and females with respect to the fatty tissue results of the VM and VI muscles (p>0.05).

**Connective Tissue**

Generally, the connective tissue in the VM muscle was determined at a significantly greater rate than in the VL and VI muscles (p=0.018).

**Table 1. The ratio of atrophic muscle cells to healthy muscle cells**

Muscle from which biopsy was taken	Maximum-minimum	Median	Mean ± SD
Vastus lateralis	5.3%-29.6%	17.2%	16.8%±5.6%
Vastus medialis	5.0%-25.4%	18.0%	17.7%±5.2%
Vastus intermedius	4.1%-26.7%	16.3%	16.5%±5.5%

SD: Standard deviation

**Table 2. Correlations between the varus angle and the atrophic cell ratio**

		Atrophic muscle cell ratio		
		VL	VM	VI
Varus angle	r	-0.035	0.436	0.386
	p	0.853	0.013	0.029

VL: Vastus lateralis, VM: Vastus medialis, VI: Vastus intermedius

No significant difference was observed between males and females with respect to the connective tissue results of the VL, VM and VI muscles ( $p>0.05$ ).

### Correlations Between Atrophic Muscle Cell Ratios and the Amounts of Fatty and Connective Tissue

In the VL muscle, no statistically significant difference was seen between the fatty tissue and the atrophic muscle cell ratios in the absent-mild group and the moderate-severe groups ( $p>0.05$ ). In the VM muscle, the atrophic muscle cell ratio was significantly higher in the moderate-severe fatty tissue group than in the absent-mild fatty tissue group ( $p<0.05$ ). In the VI muscle, the atrophic muscle cell ratio was significantly higher in the moderate-severe fatty tissue group than in the absent -mild fatty tissue group ( $p<0.05$ ).

No significant difference was determined in the atrophic muscle cell ratios between the groups with absent-mild and moderate-severe connective tissue in the VM, VL, and VI muscles ( $p>0.05$ ) (Table 3).

	Fatty tissue absent-mild		Fatty tissue moderate-severe		p
	Mean $\pm$ SD %	Median %	Mean $\pm$ SD %	Median %	
<b>Atrophic muscle cell ratio</b>					
VL	16.55 $\pm$ 8	13.1	17.65 $\pm$ 5	19.2	0.255
VM	14.75 $\pm$ 8	16.0	19.24 $\pm$ 4	20	0.031
VI	12.65 $\pm$ 0	11.3	18.74 $\pm$ 6	18.2	0.006

VL: Vastus lateralis, VM: Vastus medialis, VI: Vastus intermedius, SD: Standard deviation

## DISCUSSION

In this study, examinations were made on knees with grade 4 gonarthrosis, varus alignment, and severe pain. The quadriceps muscle sections were evaluated separately, to determine whether there was any correlation between the atrophy of the sections and varus alignment.

The lower extremity muscles provide functional stability of the knee joint and function as a shock absorber (7). In a knee with normal alignment, quadriceps strength is not related to osteoarthritis. However, greater strength or weakness of the quadriceps in the presence of malalignment or laxity is associated with the progression of knee osteoarthritis (8). If the strength of the quadriceps muscle weakens, the rate of loading formed in the knee is higher (7).

Noehren et al. (3) reported that in the pathological examinations of the quadriceps muscle in knees with a moderate degree of osteoarthritis, the extracellular matrix is increased and the regeneration capacity of the muscle in these knees is significantly reduced compared with the knees of healthy individuals. The quadriceps muscle strength decreases with an increase in the stores of fibrotic collagen in the muscles (3). In animal models, muscle strength is decreased by excessive fibrosis (9). Corresponding to an evident decrease in satellite cells in patients with osteoarthritis, fibrosis is increased in the extracellular matrix (3). To evaluate quadriceps atrophy in the current study, pathological evaluations were made of the amount of fibrosis and fatty tissue in the muscle and the ratio of atrophic muscle cells to healthy muscle cells. The results showed that the amounts of connective tissue in the VM muscle was significantly greater than in the VL and VI muscles ( $p=0.018$ ).

Although the findings of the risk of the development of osteoarthritis are controversial in patients with strong quadriceps muscles and malalignment or those with knee laxity (8,10,11), increased quadriceps strength prevents cartilage degeneration on the lateral surface of the patella-femoral compartment (10). Impaired activation of the quadriceps muscle additional to osteoarthritis is usually associated with a decrease in sensory receptors in the knee joint because stimulation of alpha motor neurons was reduced with spinal and/or supraspinal mechanisms in these patients (7).

In a prospective cohort study magnetic resonance imaging (MRI) examinations, it was reported that when the quadriceps muscle is strong, cartilage loss in the lateral patella-femoral joint is reduced, but there is no effect on cartilage loss in the tibiofemoral joint. The presence of a strong quadriceps muscle has a chondroprotective effect (10). In another later cohort study, females with normal knee alignment were followed up for 30 months, and the study reported a correlation between the weak quadriceps muscle and increased narrowing of the joint space (12). The ratio of hamstrings to quadriceps has not been shown to affect the narrowing of the joint in males or females (12).

Lim et al. (13) examined the electromyographic (EMG) activity of quadriceps muscles in patients with knee osteoarthritis. There is not found to be any relationship between the ratio of the VM to the VL and the peak quadriceps torque and severity of varus malalignment of the knee. The EMG of the VM was found to be greater than that of the VL, and the mean VM/VL ratio is approximately 1.3 (13).

MRI examinations have found the VM/VL ratio to be higher in varus knees than in neutral or valgus knees (14). During the flexion-extension movement of the knee in individuals with no

pain, the ratio of VM obliquus and VL activity is almost 1:1 (15).

Malalignment of the joint and excessively disproportional axial loading on the knee joint may be found in the pathogenesis of the formation of knee osteoarthritis. In knees with malalignment (deviations of  $>5^\circ$  from the mechanical axis), there is an increase in loading on the quadriceps, which increases knee laxity (defined as a varus-valgus deviation  $>6.5^\circ$ ) (4). Therefore, unbalanced loading on the joint leads to focal stress in the joint.

Disproportionately increased loading in the joint in the frontal plane causes progressive cartilage loss and deformity in the medial or lateral joint surfaces of the knee (14). While varus alignment increases the risk of progression of medial osteoarthritis, valgus alignment increases the progression of lateral osteoarthritis. Also, varus or valgus alignment exceeding  $5^\circ$  can cause functional impairment in a short period of 18 months (1). Among patients included in the current study, the mean varus angle of the knees was  $12^\circ$ .

Malalignment of the knee affects the external knee moment in the frontal plane during walking. Apart from the bone and joint geometry, the alignment the knee depends on the strength of the muscles around the knee or joint laxity. Of these factors, muscle strength can be modified and is reversible. Quadriceps weakness is a well-known risk factor in the development and progression of gonarthrosis (14), so strengthening of the quadriceps is important in the rehabilitation of gonarthrosis.

In MRI examinations, the VM/VL ratio is significantly higher in varus knees than in neutral or valgus knees (10). A previous study has shown that gender affects medial and lateral osteoarthritis, with lateral osteoarthritis seen more in women (16). In this study, the ratio of fatty tissue in the VL muscle was found to be significantly higher in females than in males. This greater amount of fatty tissue in the VL muscle in females could indicate greater weakness in the VL muscle and could therefore be a reason for osteoarthritis. The more frequent observation of lateral osteoarthritis in females could be explained by the more frequent observation of valgus alignment in females (17,18). In contrast, Brouwer et al. (19) reported that while varus malalignment was associated with the development of osteoarthritis, the effect of valgus malalignment

On deviations of more than  $5^\circ$  from the mechanical axis, there is an increase in loading on the quadriceps, which increases knee laxity (defined as a varus-valgus deviation  $>6.5^\circ$ ) (4). Therefore, unbalanced loading on the joint leads to focal stress in the joint.

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This muscle weakness is seen particularly in the early stages of osteoarthritis. It may have been present before the onset of the disease (4). Quadriceps muscle strengthening exercises are a treatment approach recommended by some authors. A strong quadriceps muscle is important in pain control. However, this patient group is composed of the elderly, and a widespread decrease in muscle mass with aging is expected (21).



## Study Limitations

There were some limitations to our study. Biopsy samples were taken from fresh cadavers with varus alignment but no gonarthrosis used as a control group. Another limitation was the wide confidence intervals in some analyses, which was due to the small sample size. The findings of this study highlight the need for further research. Evaluations of muscle atrophy in gonarthrosis at earlier stages while determining the relationship with alignment would be especially helpful in revealing the progression of atrophy (cadaver studies). If it can be shown how muscle atrophy progresses and which quadriceps muscles are affected in the early stage of osteoarthritis, treatment directed to this pathology may be useful in decreasing pain, slowing disease progression, and increasing quadriceps muscle capacity.

Muscle weakness is been well defined and accepted in knees with osteoarthritis, but the measurement is not easy, and it has not always been well reported in osteoarthritis studies.

## CONCLUSION

In conclusion, in this study, the histopathological analysis was applied to VM, VL, and VI muscles, taken from patients with gonarthrosis. The frequency of structural changes was analyzed in addition to atrophy and associations were examined with clinical parameters, such as the alignment of the knee.

The amount of fatty tissue and fibrosis is important in the determination of muscle atrophy, as these are indicators of poor muscle quality. The results of the current study showed that with an increase in varus angle, there was observed be a significant increase in the ratio of atrophic cells in the VM and VI muscles. Muscle rehabilitation plays an important in gonarthrosis treatment. Good rehabilitation increases joint integrity, reduces symptoms and prevents disease progression. Rehabilitation directed to the VM muscle, which is atrophic and weak, will improve symptoms and correct the joint structure. The current study results demonstrated a significantly greater amount of fatty tissue and fibrosis and atrophic cell ratio in the VM muscle compared to the VL and VI. Atrophy in the VM and VI was seen to increase in correlation with the varus angle. Atrophy in the VL muscle did not show a correlation with the varus angle (Table 2). Therefore, it would be more appropriate to apply physical therapy directed to the VM, in particular, to prevent muscle fibrosis in varus knees.

## Ethics

**Ethics Committee Approval:** Approval for the study was obtained from the Giresun University Faculty of Medicine Local

Research Ethics Committee (decision date: 21.06.2017, number of decisions: 8).

**Informed Consent:** Informed written consent was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: K.A., C.Z.E., Concept: C.Z.E., Design: İ.Ç., K.A., D.E., Data Collection or Processing: İ.Ç., K.A., Analysis or Interpretation: İ.Ç., C.Z.E., Literature Search: D.E., Writing: İ.Ç., D.E., C.Z.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Comparison of Maximal Bite Force in Children Undergoing Adenotonsillectomy: A Prospective Case-control Study with 6-month Follow-up

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## Abstract

**Objective:** This study investigated the early and late postoperative maximal bite force (MBF) values in pre-pubertal children undergoing adenotonsillectomy (AT) and compared them with healthy control.

**Methods:** A total of children aged 6-12 years, diagnosed with chronic obstructive adenotonsillar hypertrophy (COATH), undergoing AT (n=30), and healthy controls (n=30) were included. The MBF and body mass index (BMI) were recorded for up to sixth months. The duration of active surgery was recorded. The visual analog scale (VAS) was applied to the patients for the pain on postoperative first and seventh days.

**Results:** There was no significant difference in MBF values between the groups from the baseline to sixth month ( $p>0.05$ ). A statistically strong positive correlation was observed between MBF and age ( $p<0.05$ ). A significant difference was observed in MBF changes in patients with duration of active surgery more than 20 min compared with those with less from the baseline to the first month ( $p<0.05$ ). In the study group, it was observed that there was a low and moderate correlation in the mean changes between the MBF and BMI in the first, 7<sup>th</sup> day, and 1<sup>st</sup>-month matches ( $p<0.05$ ). The VAS scores did not show a significant correlation with the MBF values ( $p>0.05$ ).

**Conclusion:** The COATH and sex did not have a significant effect on MBF in pre-pubertal children, but age did. The postoperative MBF values were reached in the 1<sup>st</sup> month almost baseline values and there was a rapid increase between three and six months after AT. The prolonged operative time may affect MBF during one month postoperatively.

**Keywords:** Bite force, adenotonsillectomy, temporomandibular joint, pain, biting



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**Received:** 19.11.2021  
**Accepted:** 08.01.2022

**Cite this article as:** Atar Y, Atar S, Dıraçođlu D, Üstün O, Kumral TL, Aydođdu İ, Tutar B, Sarı H, Ahmed EA, Uyar Y, Berkiten M, İnan M. Comparison of Maximal Bite Force in Children Undergoing Adenotonsillectomy: A Prospective Case-control Study with 6-month Follow-up. Eur Arch Med Res 2022;38(4):268-274

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European Archives of Medical Research published by Galenos Publishing House.

## INTRODUCTION

Adenotonsillectomy (AT) is one of the most common surgeries performed during childhood. The most important complications that surgeons deal with include postoperative pain and bleeding (1). Besides these, temporomandibular joint (TMJ) dislocation, tooth loss, mandible condyle fracture, masseter muscle (MM) tenderness, and tooth enamel fracture have been reported due to the use of a mouth retractor (2).

Chronic diseases of the adenoid and tonsils, hypersomnia with sleep apnea, and adenoid vegetation (AV) are among the indications, although chronic obstructive adenotonsillar hypertrophy (COATH) has come to the fore recently (3). Growth and development decrease in children who suffer from COATH compared with their healthy peers (4).

Maximal bite force (MBF) is defined as the maximum force applied by a person while deliberately biting through an object. In childhood, the relationship between MBF with masticatory dysfunctions, occlusal condition, maxillofacial morphology, and demographic factors has been shown in previous studies (5,6-9).

A mouth gag was used during the AT to provide a better view of the tonsillar fossa and to fix the mouth opening. However, the view may change according to the condition of the masticatory and oro-dental structures such as TMJ, MM, mandibular body, teeth, and accordingly, more or less force can be applied through the mouth gag. The mouth gag used during AT may affect these structures, which allow the biting and chewing function.

The MBF measurements are used in studies conducted on orthodontic interventions and structural factors that cause pain in TMJ and MM (5,7,8,10,11). Studies have shown that MBF values are positively correlated with many parameters such as nutrition, chewing, breaking down solid foods, sleep, and oral health (5,7,8,12,13). As far as it is known, although many studies have investigated the effects of both AT and COATH on the quality of life and growth development, there is no study in which MBF is an objective evaluation parameter and compared with body mass index (BMI) changes after the AT.

For a purpose that it may be a reference study to predict the effects of other transoral surgeries as long-term the mouth opening, we conducted a study consisting of the pre, early and late postoperative MBF measurements, which were measured using a bite force recorder (BFR), in pre-pubertal pediatric patients COATH undergoing AT and compared them their demographics, operative times and healthy controls.

## METHODS

The study was approved by the University of Health Sciences Turkey, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Ethical Committee (decision no: 2015/03/05, protocol code: 2015/25) and performed according to the Declaration of Helsinki. At the start of the study, it was determined that a minimum of 30 participants would be needed for each group (1:1), with a 5% difference and 85% power. It was performed on 30 children (group 1) diagnosed with COATH who planned to have AT and 30 age and gender-matched healthy children (group 2). All the participants and their parents were informed about the study, and they provided written informed consent. The participants were detailed examined by an ear nose throat surgeon and a dentist. Prepubertal children aged 6-12 years with angle class I molar relationship without extracted or restored teeth, open bite, or crossbite were included in the study. Those who have had AT surgery with diagnoses other than COATH, maxillofacial trauma, known TMJ dysfunctions, intellectual disability, syndromic disease, malignancy, neuromuscular disease, craniofacial abnormality, tooth loss or mobility, gingival infection, asthma, having class II-III malocclusion, morbid obesity, dental coating, fillings or suspenders, having dental caries on first permanent molars, coagulation disorders, revision surgery were excluded from the study.

All participants underwent fiberoptic nasal endoscopic examination to estimate AV size. The size of the adenoid was determined and the distance of the adenoid tissue from the vomer was assessed and graded as grade I: Distance >1 cm, grade 2: Distance 0.5-1.0 cm, grade 3: Distance <0.5 cm (14). In the examination, the size of the tonsillar hypertrophy (TH) was evaluated Friedman's classification. The children with FC sizes 3 or 4 TH and grade 2-3 AV were included in group 1 and the children who had other low grades were included in group 2. Subsequently, a dentist examined the occlusion, mouth opening, TMJ function, and MM sensitivity of all patients. During the study, the weight and height were measured in the morning times before breakfast, and BMI (kg/m<sup>2</sup>) was calculated.

In group 1, the patients were operated on by the same surgeon, and a classic cold knife AT was performed. During the surgery, Boyle-Davis mouth gag (in sizes suitable for the age of the child) and tongue blade equipment were used by hanging on the operating table-fixed visor. The time from the moment the mouth retractor was opened in the mouth to when it was removed from the mouth was recorded in minutes [duration of active surgery-(DAS)]. The same anesthetic drugs and acetaminophen were administered to all the patients.

MBF values were measured using a BFR, which was placed in the mid incisor with left and right molar area. The subjects were asked to bite as strongly as they could. A total of three measurements were made for each patient from the left and right molar sensors in each session, a 10-minute rest was taken between measurements, and the highest value was recorded. The reliability of this device for MBF measurements has been demonstrated both *in vitro* and *in vivo* (9,13). The device recording the bite force using three strain gauge (Model 13; Honeywell Sensotec, Columbus, OH, USA) was placed between 0.85 mm thick stainless-steel plates; its output was amplified by an amplifier (AD627; Analog Devices, Norwood, MA, USA); and the values were analyzed by computer, using a software (HOBOWare; Onset Computer, Bourne, MA, USA) (Figure 1).

Six times measurements for the study group and four times measurements for the control group were made, which are as follows: Before the operation, on the 1<sup>st</sup>, 7<sup>th</sup> days, and 1<sup>st</sup>, 3<sup>rd</sup>, and 6<sup>th</sup> months after the AT in the study group; in the control group, baseline, and on the 1<sup>st</sup>, 3<sup>rd</sup>, and 6 months were made.

The visual analog scale (VAS) was used to rate the pain. Using the faces pain rating scale, the patients were instructed to point to the position on the line between the faces to indicate how much



**Figure 1.** The dental apparatus of the bite force recorder device, designed to be suitable for the incisor and molar tooth sections, and the unit that amplifies the bite force data are shown

pain they felt. On postoperative days 1 and 7, they were asked to rate their pain on a VAS diagram.

### Statistical Analysis

All statistical analyses were performed using SPSS version 17 (IBM, SPSS, Turkey). Chi-square or Fisher's exact tests were used to compare categorical variables. Correlation coefficients and statistical significance were calculated with the Pearson test for relationships between parametric variables, of which at least one is not normally distributed or ordinal. In addition to descriptive statistical methods, a repeated ANOVA test was used to compare repetitive parameters with normal distribution for the comparison of quantitative data. Post-hoc Bonferroni test was used to evaluate the differences between the groups. Student's t-test was used to compare independent parameters. A p value of <0.05 was considered statistically significant.

## RESULTS

The mean ages of group 1 and group 2 were  $8.43 \pm 2.25$ ,  $8.50 \pm 1.83$ , respectively ( $p=0.900$ ). The gender ratio (F/M) in groups 1 and group 2 was 0.66 and 0.58, respectively ( $p=0.791$ ). The mean BMI of group 1 and group 2 were  $19.05 \pm 3.54$ ,  $19.82 \pm 3.14$ , respectively ( $p=0.386$ ).

In group 1, there were 27 grade 3 AVs and three grade 2 while in group 2, all of the AV sizes were grade 1. In group 1, there were 26 size 4 THs and four size 3 while in group 2, 23 size 1 THs and seven size 0. In group 1, 28 children had complaints of sleep with open mouth and snoring, while the other group did not have these complaints except for one child. The mean DAS was  $20.7 \pm 3.03$  min.

There was no statistical difference in mean BMI values between the groups from the baseline to 6<sup>th</sup> month except the 1<sup>st</sup> month (Table 1).

No significant difference was observed in baseline MBF values between genders ( $p=0.975$ ). The correlation between baseline MBF values according to age was evaluated. There was a statistically strong positive correlation between MBF and age ( $R=0.929$ ,  $p=0.001$ ). There was no statistical difference in mean MBF values between the groups at the baseline ( $p=0.170$ )

MBF measurements differed significantly within group 1 according to the postoperative follow-up, and group 2 ( $p<0.001$ ). The post hoc test revealed that the decrease in measurements on both days 1 and 7 was statistically lower than the preoperative measurement in group 1 ( $p<0.001$ ). No difference was observed between the preoperative measurement and the postoperative measurement in 1<sup>st</sup> month ( $p=0.962$ ). In 3<sup>rd</sup> and 6<sup>th</sup> months, the

Timeline	Mean MBF (n) ± SD				
	Group 1	p*	Group 2	p*	p**
Baseline	317.49±71.54	NA	341.25±60.54	na	0.170
1 <sup>st</sup> day	265.87±69.19	<0.001	NA	NA	NA
7 <sup>th</sup> day	279.39±68.10	<0.001	NA	NA	NA
1 <sup>th</sup> month	317.58±71.30	0.962	342.45±61.22	0.136	0.152
3 <sup>rd</sup> month	336.80±73.55	<0.001	349.52±62.81	<0.001	0.474
6 <sup>th</sup> month	365.42±77.10	<0.001	366.20±64.90	<0.001	0.967
p***	<0.001	-	<0.001	-	-
<b>Mean MBF change (n) ± SD</b>					
1 <sup>st</sup> day†	-52.19±17.18	NA	NA	NA	NA
7 <sup>th</sup> day†	-38.09±15.19	NA	NA	NA	NA
1 <sup>th</sup> month†	0.92±10.39	NA	1.21±4.33	NA	0.588
3 <sup>rd</sup> month†	19.31±6.85	NA	8.28±5.75	NA	<0.001
6 <sup>th</sup> month†	47.93±10.37	NA	24.95±6.87	NA	<0.001
<b>Mean BMI (kg/m<sup>2</sup>) ± SD</b>					
Baseline	19.05±3.54	NA	19.81±3.14	NA	0.386
1 <sup>st</sup> day	19.03±3.51	0.426	NA	NA	NA
7 <sup>th</sup> day	19.02±3.52	0.107	NA	NA	NA
1 <sup>th</sup> month	18.46±3.43	<0.001	19.89±3.10	0.109	0.033
3 <sup>rd</sup> month	18.92±3.34	0.067	19.98±3.17	0.064	0.214
6 <sup>th</sup> month	19.49±3.48	<0.001	20.38±3.58	0.034	0.327
p***	0.001	-	-	-	0.151
<b>Mean BMI changes (kg/m<sup>2</sup>) ± SD</b>					
1 <sup>st</sup> day†	-0.26±0.18	NA	NA	NA	NA
7 <sup>th</sup> day†	-0.36±0.12	NA	NA	NA	NA
1 <sup>th</sup> month†	-0.59±0.33	NA	0.06±0.21	NA	<0.001
3 <sup>rd</sup> month†	-0.13±0.38	NA	0.16±0.40	NA	0.005
6 <sup>th</sup> month†	0.43±0.47	NA	0.66±0.180	NA	0.416
p*: Paired t-test, p**: Independent t-test, p***: ANOVA test p<0.05, †: Difference between last value - baseline value, MBF: Maximal bite force, BMI: Body mass index, NA: Not applicable, SD: Standard deviation					

MBF measurements were found to be significantly higher than the baseline measurement in both groups ( $p < 0.001$ ). There was no significant difference in the mean MBF values from groups 1 and 2 (Table 1). There were also shown mean MBF and BMI values and their changes in Table 1.

MBF measurements were also evaluated in terms of the length of surgery. DAS shorter than 20 min ( $n=14$ ) and those longer than 20 min ( $n=16$ ) were compared. The pre-and postoperative MBF measurements are shown according to the DAS in Table 2.

At the baseline, the MBF values did not show a significant correlation with the BMI values in the groups 1 and 2 ( $R=0.137$ ,  $p=0.472$ ;  $R=0.168$ ,  $p=0.375$ , respectively). A correlation chart was shown between MBF and BMI values for group 1 in Table 3.

On postoperative day 1, the VAS scores did not show a significant correlation with the MBF values ( $R=-0.262$ ,  $p=0.163$ ). On a postoperative day 7 as well, the VAS scores did not indicate a significant correlation with MBF values ( $R=-0.329$ ,  $p=0.078$ ).

## DISCUSSION

A proper masticatory system stimulates the normal development of the maxilla and mandible. The three years before the initiation of mixed dentition are crucial, as normal growth changes and functional adaptability occur during this period (15). In children, the peripheral sensorimotor pathways underlying the jaw-stretch reflex mature as the child continues to obtain oral motor skills (16). AT is the most frequently performed surgery at this age.



**Table 2. Comparison of MBF measurements in terms of duration of active surgery in the study group (group 1)**

Timeline	Mean MBF (n) ± SD		P
	≤20 minutes (n=14)	>20 minutes (n=16)	
Baseline	318.88±66.36	316.26±77.94	0.922
1 <sup>th</sup> day	276.48±62.80	255.49±74.96	0.416
7 <sup>th</sup> day	289.48±63.45	270.57±72.79	0.458
1 <sup>th</sup> month	323.58±63.08	312.32±79.49	0.674
3 <sup>rd</sup> month	339.14±68.44	334.75±79.93	0.874
6 <sup>th</sup> month	368.49±75.68	362.73±80.69	0.842
Mean MBF change (n) ± SD			
1 <sup>th</sup> day†	-42.39±9.49	-60.77±18.02	<b>0.002</b>
7 <sup>th</sup> day†	-29.41±15.19	-45.69±14.51	<b>0.002</b>
1 <sup>th</sup> month†	4.69±4.55	-3.93±12.40	<b>0.020</b>
3 <sup>rd</sup> month†	20.26±8.03	18.49±5.77	0.490
6 <sup>th</sup> month†	49.60±13.11	46.47±7.34	0.419

†: Difference between last value - baseline value, t-test p<0.05, MBF: Maximal bite force, SD: Standard deviation

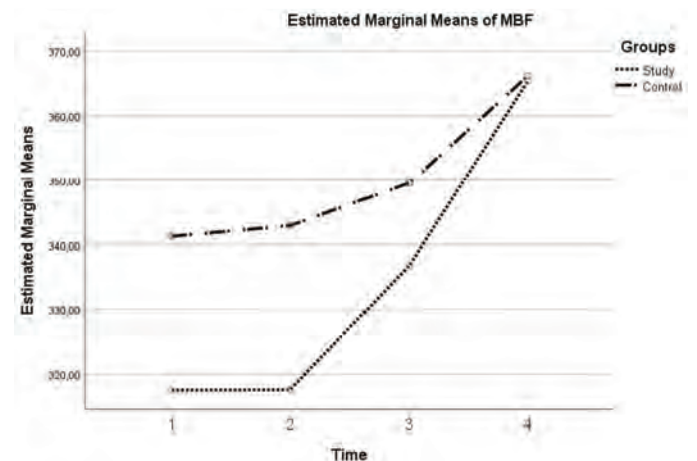
During the operation, a Boyle-Davis mouth gag is used, which ensures that the patient's mouth remains in the maximum open position; however, this apparatus is a challenge for the TMJ and masticatory muscles.

MBF is an objective and quantitative measurement used to evaluate masticatory performance (13,17). It has been shown in previous studies that MBF was negatively affected by several TMJ diseases, masseteric silent period, masticatory dysfunctions (7,18,19). For this reason, in this study, we compared MBF values by preoperative, early, and late postoperative periods and observed that these values decreased significantly in the early period after the operation but approached the preoperative values in 1<sup>st</sup> month.

Bite force follows an increasing trend since childhood, remains stable between the ages of 20 and 40 years, and then begins to decline (20,21). Facial structure, the gender difference in post-puberty, general muscular force, dental condition, malocclusion, and TMJ disease also affect MBF (22,23). In this study, it was found significant that MBF increased as age increased. Previous studies showed that MBF in the pre-pubertal period was similar in both genders due to yet undifferentiated maxillofacial muscles and jaw structures. Similarly, in this study, there was no significant difference noted between the two genders. In another study, it was reported that the history of mouth breathing in children did not have a significant effect on MBF (24). In this study, there was no difference between the baseline MBF values of both groups of children with a diagnosis of COATH and the healthy control group.

Hatch et al. (25) reported that MBF was directly related to masticatory performance, but it was not as effective as the number of functional teeth. Julien et al. (26) found that MBF, along with occlusal contact area and body size, explained 72% of the variation in masticatory performance among children and adults. Lepley et al. (18) investigated the effects of occlusion, MBF, and chewing cycle kinematics on masticatory performance and found that occlusal contact area and occlusal discrepancies are related to bite force and chewing cycle kinematics. They also found that MBF was positively associated with masticatory performance. Despite all these reports on nutrition and solid food chewing, no significant correlation was reported between BMI and MBF (3,5,18,25,26). In this study, there was no correlation between MBF and BMI. Unlike the evaluations of these studies, it was observed that there was a weak or moderate correlation between MBF and BMI changes in the 1<sup>st</sup> three months postoperatively.

Additionally, although all patients had full dentulous and normal occlusion, those with TMJ who remained fully open for more than 20 min showed a significant difference in mean MBF changes over one month compared to those with shorter periods. However, the average MBF values rose rapidly after 3 months, approximating the control group values with a slight difference (Figure 2). There was no significant correlation between VAS scores and MBF values on postoperative days 1 and 7. It showed that during the early postoperative recovery period of AT, regardless of other factors such as inflammation and pain that might affect the bite force, the force applied by the mouth gag to the TMJ alone decreases MBF. However, a significant difference in month mean BMI values between the two groups on 1<sup>st</sup> month made us think that the reduction in MBF was a



**Figure 2.** The course of mean MBF values in the study (group 1) and control (group 2) groups  
MBF: Maximal bite force

**Table 3. The relationship between MBF and BMI values on postoperative days one, seven, and months one, three and six in the study group**

Mean BMI change										
Mean MBF change	1 <sup>st</sup> day		7 <sup>th</sup> day		1 <sup>st</sup> month		3 <sup>rd</sup> month		6 <sup>th</sup> month	
	R	p	R	p	R	p	R	p	R	p
Postoperative 1 <sup>st</sup> day	0.494	<b>0.005</b>	0.513	<b>0.004</b>	0.583	<b>0.001</b>	0.518	<b>0.003</b>	0.137	0.470
Postoperative 7 <sup>th</sup> day	0.499	<b>0.005</b>	0.456	<b>0.011</b>	0.478	<b>0.008</b>	0.425	<b>0.019</b>	0.164	0.386
Postoperative 1 <sup>st</sup> month	0.592	<b>0.001</b>	0.652	<b>&lt;0.001</b>	0.540	<b>0.002</b>	0.296	0.112	0.161	0.394
Postoperative 3 <sup>rd</sup> month	0.113	0.551	0.277	0.139	0.019	0.920	0.097	0.612	0.031	0.873
Postoperative 6 <sup>th</sup> month	0.170	0.368	0.227	0.229	0.034	0.860	0.132	0.488	0.032	0.865

R: Pearson correlation coefficient  $p < 0.05$ , MBF: Maximal bite force, BMI: Body mass index

criterion that should not be ignored in the regulation of early post-AT nutrition.

Maini et al. (27) measured the interincisal distance in adult patients who underwent tonsillectomy surgery using a Boyle-Davis mouth gag at preoperative and postoperative week 6 and compared them with the group that had nasal surgery. In patients who underwent tonsillectomy, the interincisal distance decreased at postoperative week 6, whereas there was no significant difference in the nasal surgery group. They reported that tetanus might occur because of nerve irritation, inflammation of the pharyngeal, and spasm of the hyoid and masticatory muscles after tonsillectomy and the symptom regress took 2-3 weeks after the surgery when the relaxation of the muscles, and operation cavity was completely covered with mucosa. In this study, we had the opportunity to observe the course of the change in the post-operative MBF, which was a result of the functions of the MM and TMJ, by comparing it with the control group, beyond the effects of acute inflammation and spasm, by keeping the follow-up period long.

In several studies, it has been shown that there are functional changes in the facial muscles in the postoperative period from the first month to the sixth month in children after AT or tonsillectomy, and maxillary expansion in cephalometric measurements up to the 14<sup>th</sup> month. The reason for the increase in MBF seen in the study group from the 1<sup>st</sup> to the 6<sup>th</sup> month could be related to the results of this study, but in our methodology, a cephalometric evaluation that could compare this was not performed (28,29).

Yosetake et al. (30) compared 44 mouth breathers with upper airway obstruction between the ages of three to 12 years healthy children in terms of MBF and did not find a significant difference between the two groups. They also did not find a correlation between the degree of obstruction and MBF in mouth breathers. They reported that MBF increased with age in the healthy control

group, but that MBF did not correlate with age in patients with mouth breathing. Similarly, there was no significant difference in MBF values between the groups in our study, either before the operation or in the first month or after. However, differently, it was observed that MBF increased with age in COATH patients. The fact that participants with class I occlusion and without craniofacial anomalies were included in our study may have been beneficial to our results.

### Study Limitations

There were limitations to this study related to calibrating the BFR every week so that we could measure the measurements as accurately as possible. Although the participants with normal morphology, the fact that cephalometric measurements were excluded from our study is a limiting factor. The evaluation of puberty, the initial examination findings and the information obtained from the parents of the children were taken as reference and no additional hormone was examined.

### CONCLUSION

Children undergoing AT might experience a decrease in MBF in the acute period and this decrease could be related to the average operation time. Postoperative MBF values almost reached preoperative values in the first month and increased rapidly between three and six months after AT and reached a level significantly comparable to healthy children of the age match evaluated.

It may be useful to conduct prospective studies that include the active operation time and MBF changes during transoral surgeries in childhood.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Ethical Committee

(decision no: 2015/03/05, protocol code: 2015/25) and performed according to the Declaration of Helsinki.

**Informed Consent:** Written informed consent.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Y.A., İ.A., B.T., H.S., E.A.A., M.B., M.İ., Concept: Y.A., S.A., D.D., Y.U., Design: Y.A., S.A., D.D., O.Ü., M.B., Data Collection or Processing: S.A., İ.A., H.S., E.A.A., Analysis or Interpretation: Y.A., T.L.K., Literature Search: Y.A., O.Ü., İ.A., B.T., H.S., E.A.A., Writing: Y.A., S.A., O.Ü., T.L.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Determining the Knowledge Level and Practices of Nursing Students About Personal Hygiene and the Effect of the Training Given

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## Abstract

**Objective:** This study was conducted to evaluate the knowledge and practices of nursing students about personal hygiene and the effectiveness of personal hygiene training given to the students.

**Methods:** Bingol University Faculty of Health Sciences Nursing Department of the 2018-2019 academic year, the sample of the study was composed of n=277 students who were in the university during the data collection process and responded to the questionnaire before and after the training.

**Results:** Two hundred thirty (83.0%) of the students were female and forty-seven (17.0%) were male. When the contribution rates of the training for personal hygiene practices were examined, the first three rates were the item "I change my clothes every day" (35.7%), the item "I use cotton clothes" (30.0%), and the item "I may forget to wash my hands when I come home" (28.9%), which contributed to the nursing students.

**Conclusion:** It was seen that all students had errors and deficiencies in their attitudes and behaviors toward personal hygiene in the period before training. Positive changes occurred in the post-training period compared with the pre-training period and the participants' rates of applying personal hygiene increased.

**Keywords:** Hygiene, intervention, nursing students, training

## INTRODUCTION

Hygiene is a health science and its main concern is the protection and maintenance of health. Cleaning contributes positively to human health by protecting the body from polluting factors. It has been stated that many health problems today are related to an unhealthy lifestyle. Hospitals not only have many disease factors, but they are also an environment where many people are together. Therefore, it is a place where significant attention should be paid to hygiene (1).

Hygiene, which is a science teaching the healthy living conditions, is also a science complex that applies efficient health-related information in synthesis for the protection and development of human health and long-term continuance of life at a healthy level as an individual and society. According to the areas,

hygiene can be divided into many branches, including social hygiene, work hygiene, school hygiene, environmental hygiene and personal hygiene (2).

Personal hygiene can be defined as all practices an individual makes to keep his/her body clean and healthy. It covers health and healthy behaviors together (3).

Personal hygiene is the practice developed by a person in accordance with his/her beliefs, values and habits. Therefore, personal hygiene practices are affected by cultural, social, familial factors as well as the information level and needs of the person about health and hygiene (4).

This study aimed to evaluate the knowledge and practices of nursing students about personal hygiene and the effectiveness of personal hygiene training given to the students.



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**Cite this article as:** Bulut A, Özgüler M. Determining the Knowledge Level and Practices of Nursing Students About Personal Hygiene and the Effect of the Training Given. Eur Arch Med Res 2022;38(4):275-280

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 11.11.2020

**Accepted:** 01.04.2022

## METHODS

The study was planned in February 2019 upon the request of the nursing students. This intervention study was conducted to compare the knowledge levels of students in the Nursing Department of Bingöl University Faculty of Health Sciences regarding the personal hygiene practices. All procedures performed in the current study were in accordance with the ethical standards of the Institutional Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Bingöl University Ethics Committee (approval date and number: 15.04.2019; 92342550/044-E.8057). While the population of the study was composed of 283 students studying in the Nursing Department of Bingöl University Faculty of Health Sciences during 2018-2019 academic year, the sample the study was composed of n=277 students who were present at the university during the data collection process and responded the questionnaires before and after the training. The rate of participation in this study was 97.8%.

In data collection, a “questionnaire” with 42 questions prepared by the researchers was used. In the questionnaire prepared after the literature review, there were questions measuring the students’ socio-demographic characteristics, definition of hygiene, the use of personal hygienic products and their knowledge level about their practices for personal hygiene. The questions in the questionnaire consist of open ended and multiple-choice questions with “yes-no,” “right-wrong” answers.

The necessary permission and official correspondence from the relevant institution were completed for the application of questionnaires before training and about the planned training process and the appropriate day and time for the training was determined and necessary announcements were then made to the nursing students. After the necessary explanations and information were given to the students before starting the training, they students were asked not to write their names on the questionnaires and to mark the answers as close to their responses as possible with the aim of obtaining more realistic answers. The training program prepared for the students was then presented and the post-training part of the same questionnaire was also applied after the training.

### Statistical Analysis

The data obtained in the study were evaluated using the Statistical Program for Social Sciences (SPSS) for the Windows 22 program. In data analysis, descriptive statistics were given as number, percentage, minimum and maximum values, mean

and standard deviation. Significance was evaluated by taking  $p < 0.05$ .

## RESULTS

This study was applied to 277 nursing students. Two hundred thirty (83.0%) of the students were female and forty-seven (17.0%) were male. The mean age of the students was 21+/-2 years. Of the students, 74 (27.0%) were 1st-year students, 72 (26.1%) were 2nd-year students, 65 (23.1%) were 3rd-year students, and 66 (23.8%) were 4<sup>th</sup>-year students.

To the question “the place where you have lived for the longest time,” 66 (23.8%) of the students stated a village, 17 (6.2%) as town, 53 (19.1%) as districts, and 141 (50.9%) as provinces. When their parents’ education levels were questioned, 141 (50.9%) of the mothers were illiterate, 89 (32.1%) were primary school level, 12 (4.3%) were secondary school level, 3 (1.1%) were high school level and 3 (1.1%) were university and higher education level. When their fathers’ education levels were questioned, 32 (11.6%) of the fathers were illiterate, 19 (6.9%) were literate, 127 (45.8%) were primary school, 38 (13.7%) were secondary school, 44 (15.9%) were high school, and 17 (6.1%) were university and higher education level. It was determined that 214 (77.3%) had a nuclear family type, 61 (22.0%) had extended families and 2 (0.7%) had a broken family structure (Table 1).

Table 2 shows the questions asked the students about the use of personal hygiene products and their answers.

Before providing the training to the students to get information about personal hygiene practices, various questions were asked to them. Table 3 shows personal hygiene practices before and after training.

Post-training responses of the students who responded negatively to the questions before training were evaluated again and the students whose negative practices turned to positive practices were examined again. Table 4 shows the contribution rates of training for personal hygiene practices.

## DISCUSSION

Personal hygiene is the most important factor for people to lead a trouble-free life away from diseases. Personal hygiene activities are conducted to prevent most diseases, particularly epidemics. These activities include washing the hands and face, having a proper bath, washing the hands with soap and clean water after the toilet, washing the hands when cooking, before and after eating, keeping the nails clean, brushing the



**Table 1. Distribution of the participants socio-demographic characteristics (n=277)**

Socio-demographic characteristics	Number (n)	Percentage (%)
<b>Gender</b>		
Female	230	83.0
Male	47	17.0
<b>Mean age</b>		
21+/-1.5 (min: 18-max: 32)		
<b>The place where you have lived for the longest time</b>		
Village	66	23.8
Town	17	6.1
District	53	19.1
Province	141	50.9
<b>Mother's education level</b>		
Illiterate	141	50.9
Literate	29	10.5
Primary school	89	32.1
Secondary school	12	4.3
High school	3	1.1
University and higher	3	1.1
<b>Father's education level</b>		
Illiterate	32	11.6
Literate	19	6.9
Primary school	127	45.8
Secondary school	38	13.7
High school	44	15.9
University and higher	17	6.1
<b>Presence of siblings</b>		
Yes	265	95.7
No	12	4.3
<b>Number of siblings</b>		
No siblings	9	3.2
<5 siblings	176	63.5
6-10 siblings	87	31.4
11-15 siblings	3	1.1
>16 siblings	2	0.7
<b>Total</b>	277	100

teeth, washing the feet, hair cleaning and care, and keeping the personal shoes, towel, laundry, brushes, and slippers clean (5,6). When all personal hygiene practices are examined, not only the body cleaning but also cleaning the environment and items used in hygiene practices and their personal use are important. According to the results of the study by Aydın (7), 94.7% of the primary school students had their own toothbrushes. In a study by Irmak (8), 91.6% of the patients had a personal toothbrush, whereas 8.4% did not. In the study by Kaya et al. (9), to determine the behaviors of students from a high school in Ankara about personal hygiene, 100% of the students stated that they had their own underwear and toothbrushes and 43.2% had their own nail clippers.

Personal hygiene is obtained in accordance with the person's beliefs, value judgments and habits. Thus, personal hygiene applications are affected by not only cultural, familial and social factors, but also by the person's need for health and hygiene and their personal training (10). Before the training was given to the students to get information about their personal hygiene practices, various questions were asked to them. Their responses before and after the training were then compared. Washing hands after the toilet was found to be 98.9% in the study by Şahin et al. (11). In the study by Thumma et al. (12) with the students staying in student dormitories, 84% of the students stated that they washed their hands every time after using the toilet. In another question, while 50.5% of the participants selected the "always" option to the item "I should brush my teeth at least twice a day" before training, 69.3% selected "always" after training. In the study performed by Sefit (13), 29.9% of the university students brushed their teeth twice a day. In the study by Silva et al. (14), entitled as "oral health of quilombola and quilombola rural adolescents: Investigation of hygiene habits

**Table 2. Distribution of the participants according to the usage status of personal hygiene products (n=277)**

Hygiene product	Used only by me		Used by whole family		I never use		Total n (%)
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)	
Razor	138	49.9	4	1.4	135	48.7	277 (100)
Toothbrush	264	95.3	13	4.7	0	0	277 (100)
Socks	236	85.2	41	14.8	0	0	277 (100)
Nail clipper	157	56.7	120	43.3	0	0	277 (100)
Comb	185	66.8	87	31.4	5	1.8	277 (100)
Underwear	266	96.0	11	4.0	0	0	277 (100)
Hand towel	134	48.3	141	50.9	2	0.8	277 (100)
Shoes/slippers	215	77.6	61	22.0	1	0.4	277 (100)
Bath towel	208	75.1	68	24.5	1	0.4	277 (100)
Banyo washcloth	218	78.7	52	18.8	7	2.5	277 (100)
Bathroom slippers	100	36.1	177	63.9	0	0	277 (100)

**Table 3. Distribution of students' practices regarding the personal hygiene (n=277)**

Hygiene application	Always (before training)		Always (after training)		Sometimes (before training)		Sometimes (after training)		Never (before training)		Never (after training)	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)
I should wash my hands when I wake up	261	94.3	266	96.0	15	5.3	4	1.5	1	0.4	7	2.5
I should wash my face when I wake up	265	95.7	261	94.3	12	4.3	9	3.2	0	0	7	2.5
I should wash my face before going to bed	121	43.7	190	68.6	144	52.0	73	26.4	12	4.3	14	5.1
I should clean my nose with water	133	48.0	162	58.5	138	49.9	99	35.7	6	2.2	16	5.8
I should wash my hands before and after eating	192	69.3	227	81.9	83	30.0	36	13.0	2	0.7	14	5.1
After the toilet, I should wash my hands with soap	263	95.0	265	95.7	11	4.0	11	4.0	3	1.1	1	0.4
I may forget to wash my hands when I get home	34	12.3	38	13.7	165	59.6	107	38.6	78	28.2	132	47.7
I have just washed my hands with water	20	7.2	50	18.1	116	41.9	88	31.8	140	50.6	139	50.2
I should dry my hands after washing them	216	78.0	237	85.6	59	21.3	24	8.7	1	0.4	16	5.8
I should brush my teeth at least twice a day	140	50.5	192	69.3	126	45.5	72	26.0	11	4.0	13	4.7
I should use as much toothpaste as the lentil size	181	65.3	184	66.4	54	19.5	53	19.1	42	15.2	37	3.4
I should choose my toothbrush medium hard	173	62.5	202	72.9	79	28.5	61	22.0	25	9.0	14	5.1
I should change my toothbrush every 3 months	154	55.6	197	71.1	103	37.2	64	23.1	20	7.2	16	5.8
I should brush my teeth for 4 min	150	50.2	174	62.8	117	42.2	91	32.9	10	3.6	12	4.3
I should see a dentist when I have a toothache	146	52.7	95	34.3	93	33.6	116	41.9	38	13.7	66	23.8
I shouldn't use dental floss	116	41.9	82	29.6	63	22.7	86	31.0	98	35.4	108	39.0
I should cut my fingernails and toenails when they grow	235	84.8	231	83.4	35	12.6	30	10.8	6	2.2	16	5.8
I should cut my fingernails straight	127	45.9	112	40.4	57	20.6	38	13.7	93	33.6	127	45.8
I should wash my feet only in the bath	23	8.3	54	19.5	48	17.3	36	13.0	203	73.3	187	67.5
I should dry my feet after washing them	127	45.8	186	67.1	125	45.1	78	28.2	25	9.0	13	4.7

I should cut my toenails in the moon shape	110	39.7	118	42.6	89	32.1	56	20.2	78	28.2	103	37.2
I should change my socks every day	176	63.6	204	73.6	97	35.0	61	22.0	4	1.5	12	4.3
I should change my clothes every day	102	36.8	180	65.0	151	54.5	84	30.3	24	8.7	13	4.7
I should use cotton clothes	129	46.6	199	71.8	119	43.0	56	20.2	29	10.5	22	7.9
I should do my ear cleaning with a towel tip	48	17.3	100	36.1	86	31.0	58	20.9	143	51.6	119	43.0
I should use a deodorant every day for body odor	107	38.6	140	50.6	119	43.0	88	31.8	51	18.4	49	17.7

**Table 4. Contribution of training on personal hygiene practices (n=277)**

Hygiene practice	Contribution of the training (%)
*I should wash my hands when I wake up	4.3
I should wash my face when I wake up	1.1
I should wash my face before going to bed	27.1
I should clean my nose with water	15.1
*I should wash my hands before and after eating	19.5
After the toilet, I should wash my hands with soap	4.3
*I may forget to wash my hands when I get home	28.9
*I should brush my teeth at least twice a day	22.4
*I should use as much toothpaste as my lentil size	15.2
*I should change my toothbrush every 3 months	23.1
*I should brush my teeth for 4 min	18.1
*I should see a dentist when I have a toothache	9.7
*I should just wash my hands with water	15.9
*I should dry my hands after washing them	15.5
*I should cut my fingernails and toenails when they grow	11.6
*I should cut my fingernails straight	24.9
*I should wash my feet only in the bath	9.4
*I should dry my feet after washing them	27.1
*I should cut my toenails in the moon shape	22
I should change my socks every day	16.6
I should change my clothes every day	35.7
*I should use cotton clothes	30.0
I should do my ear cleaning with a towel tip	6.1
*I should use a deodorant every day for body odor	18.8
*p value was determined to <0.05	

and related factors,” 33.3% of the adolescents were seen brush their teeth three times a day.

Responses of the students who responded negatively to the questions before training were evaluated again after training and the students whose negative practices turned into positive practices were examined again. When the contribution rates of training for personal hygiene practices were examined, the first three of them were seen to be the item “I change my clothes every day” with a rate of 35.7%, the item “I use cotton clothes” with a rate of 30.0% and the item “I may forget to wash my hands when I get home” with a rate of 28.9%, which contributed to the nursing students. In the studies conducted with university students in Turkey, 38-47% of the participants changed their underwear daily (15-19). Considering these findings, it is possible to state that students are not adequately aware of the necessity of changing their underwear daily. The color, type, washing, drying and changing frequency of and storage conditions of underwear are crucial. It must choose white underwear made of cotton so that it is appropriate for boiling or washing at a higher temperature (17,20). In the study by Türkmen and Bakır (21) to evaluate the hand-washing applications of health technician candidates, 91.4% of the students stated that they washed their hands when they got home.

## CONCLUSION

It was observed that all students included in the study had mistakes and deficiencies in their attitudes and behaviors toward personal hygiene in the pre-training period. Positive changes occurred in students in the post-training period compared with the pre-training period and the participants’ rates of practicing personal hygiene increased.

In accordance with the results obtained from the study, to increase the correct information and behavior of the students, benefits and results of providing hygiene training with the right sources, such as healthcare professionals or specialists who have

special training in this field in a more planned and widespread manner, will be effective and efficient and it is recommended to add them to the curriculum. It may be useful to inform individuals through the mass media. Additionally, without ignoring the effect of families on personal hygiene practices, families should also be trained to hygiene.

## Ethics

**Ethics Committee Approval:** This study was approved by the Bingol University Ethics Committee (approval date and number: 15.04.2019; 92342550/044-E.8057).

**Informed Consent:** All participants were informed and consents forms were obtained.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: A.B., M.Ö., Concept: A.B., Design: A.B., M.Ö., Data Collection or Processing: A.B., M.Ö., Analysis or Interpretation: A.B., M.Ö., Literature Search: A.B., M.Ö., Writing: A.B., M.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Sensitization to Aeroallergens on Skin Prick Tests in Atopic Children Living in the Southwest of Turkey

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## Abstract

**Objective:** This study aimed to identify aeroallergens susceptibility patterns of atopic children living in the city of Antalya, southwest of Turkey.

**Methods:** One thousand seven hundred five patients (2-18 years) who applied to the pediatric allergy immunology outpatient clinic between April 2018-March 2020 were included in the study. The demographic and clinical characteristics of patients with at least one allergic sensitization in the skin prick test were evaluated.

**Results:** A total of 761 patients were evaluated, comprising 57.69% males and 42.31% females, with a median age of 9.25 years (range, 6.25-12.9 years). Of the total patients 54.01% had asthma (AS), 89.22% had allergic rhinitis (AR), (45.33%) had both AS and AR and 11.83% had atopic dermatitis. Sensitivity to house dust mites (HDMs) was the most common sensitivity (66.23%), followed by animal dander (39.68%) and cockroach (34.56%). Other allergens were grass pollen (32.33%), mold (31.54%), weed mixture pollen (29.04%), olive tree (27.86%), and tree mixture (14.98%), respectively. More than one allergen sensitization was detected in 537 (70.6%) patients. AR was more common in boys ( $p=0028$ ). Pollen sensitivity was higher in children with AR than in children without AR ( $p<0.001$ ).

**Conclusion:** In our study in which allergen sensitivity was determined in atopic children in our region, the most common allergens were HDMs, cockroaches and animal dander, which are indoor allergens.

**Keywords:** Aeroallergens, atopy, allergic diseases, children, sensitization

## INTRODUCTION

The prevalence of asthma and other allergic diseases (e.g., rhinitis and eczema) has increased worldwide over the last twenty years (1). The origins of these diseases are complex, but understanding genetic and environmental risk factors can shed light on possible measures which can be taken to prevent the development of the disease (2).

Atopy is an individual predisposition to the development of allergic diseases. IgE-mediated sensitization to food or at least one environmental allergen can be detected with SPT, which is an easy-to-use, fast, and highly sensitive method for diagnosing IgE-mediated allergies (3). Studies have suggested that the type of

allergen sensitization may influence the development, duration, and severity of allergic diseases (4,5). Aeroallergens are an important causal factor in the pathogenesis of these disorders, and sensitivity to allergens varies by country and region. This can be explained by differences in climate and variations in the presence of allergens in different geographical areas (6). Identifying sensitization patterns in specific geographic areas allows specific interventions such as allergen reduction and/or avoidance and encourages the use of specific immunotherapy (7). In two previous studies conducted in our region to determine childhood aeroallergens sensitivity, house dust mites (HDMs), molds and pollens were found to be the most common allergens (8,9). There may be changes in aeroallergens sensitivity over



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**Cite this article as:** Keleş Ş, Filiz S. Sensitization to Aeroallergens on Skin Prick Tests in Atopic Children Living in the Southwest of Turkey. Eur Arch Med Res 2022;38(4):281-287

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 09.01.2022  
**Accepted:** 02.04.2022



time and locally. This study aimed to evaluate the aeroallergens sensitization and its frequency in atopic children living in Antalya, southwest of Turkey by using epidermal skin prick test.

## METHODS

### Patients

This cross-sectional observational study included 1.705 patients aged 2-18 years who presented with allergic complaints and underwent SPT in the Pediatric Allergy Outpatients Clinic of University of Health Sciences Turkey, Antalya Training and Research Hospital, between April 2018 and March 2020. The demographic and clinical characteristics of 761 (44.63%) patients with at least one allergic sensitization in the SPT were evaluated. This study was conducted in concordance with ethical standards and the World Health Organization Helsinki Declaration. It was approved by the Local Ethics Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (2020, 10/16). Informed consent was obtained from all the patients.

### The Skin Prick Test

Patients were subjected to SPT for a panel of standard allergen solutions for aeroallergens (Allergopharma GmbH & Co. Hamburg/Germany), including 2 types of HDMs [Dermatophagoides pteronyssinus (Dp) and Dermatophagoides farinae (Df)], animal dander (cat epithelia, dog epithelia, horse epithelia), early and mid-term blooming tree pollens (alder, elm, hazel, poplar, willow, birch, beech, oak, plane tree), olive tree pollen, grass and cereal pollens (Kentucky blue grass, Timothy grass, Meadow fescue, Rye grass, Velvet grass, Orchard grass, Barley, Oats, Wheat, Rye) weeds (Mugwort, Dandelion, Nettle, English plantain, Wall pellitory), molds (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*), and cockroach (*Blattella germanica*). The selection of aeroallergens was based on their aerial dominance and availability.

The SPT was performed according to the international guidelines (3) as a single test on two forearms with lancets (Mizollen; H. Herenz GmbH, Hamburg/Germany) and standardized allergens. Histamine (10 mg/mL of histamine phosphate) and 0.9% sterile saline were used as positive and negative controls, respectively. The SPTs were evaluated 15 min after application and considered positive if the mean wheal diameter was  $\geq 3$  mm compared with the negative control. Patients who were sensitive to two or more classes of allergens were defined as polysensitized. House dust mite sensitivity was defined as a positive reaction to at least one of the Dermatofagoides allergens. Tree pollen sensitivity was defined as a positive reaction to at least one of the early

or middle flowering trees. Fungal sensitivity was defined as a positive response to at least one of *Alternaria alternata*, *Aspergillus Fumigatus*, or *Cladosporium herbarum*. Animal dander was defined as a positive response to at least one of the cat epitheliums, dog epithelium, or horse epithelium.

### Statistical Analysis

The SAS version 9.4 software was used for statistical analysis. Descriptive statistics were stated as mean, standard deviation, median, minimum and maximum values, or number (n) and percentage (%). The Kolmogorov-Smirnov test was conducted to check the normality distribution of independent data. Since the data were normally distributed, the Independent t-test and analysis of variance (ANOVA) were used for the comparative analysis. The chi-square test was used for the analysis of qualitative independent data. The Pearson correlation coefficient (rs) was used for correlations between parametric data. A value of  $p < 0.05$  was set as statistically significant.

## RESULTS

### Study Population

The evaluation was made of 761 children aged 2-18 years who had a positive skin prick test against at least one aeroallergens. The male/female ratio was 439 (57.69%)/322 (42.31%) and the median age was 9.25 years [6.25-12.9 interquartile range (IQR)]. Of the 761 patients, 411 (54.01%) had AS, 679 (89.22%) had AR, 340 (45.33%) had both AS and AR, 71 (9.47%) had only asthma, 339 (45.2%) had only AR, 90 (11.83%) had AD, 54 (11.61%) had only AD, and 36 (7.74%) had AD+AS.

The serum total IgE level was found to be median 209 IU/mL (78-538 IQR) in 337 patients. The eosinophil count in 352 patients was found to be mean 5.01% and median 4.3%.

More than one allergen sensitization was detected in 537 (70.6%) patients. Total IgE and eosinophil mean levels were higher in polysensitized patients (524/337,  $p=0.23$ , 5.25%/4.35%  $p=0.036$  respectively). *Alternaria alternata* was the most common sensitivity in monosensitized patients (2.3%), followed by Df (1.97%), and Dp (0.53%).

### Prevalence of Aeroallergens Sensitization

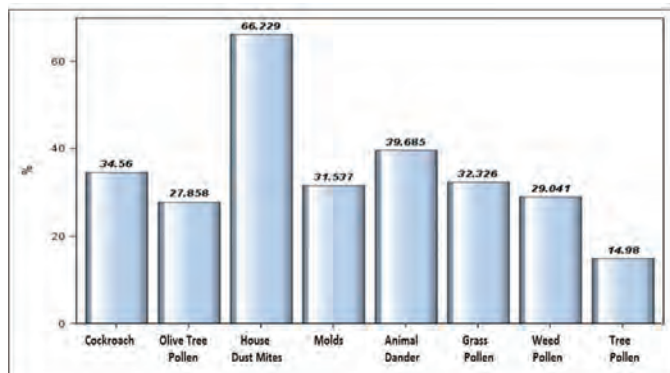
Sensitivity to HDMs was the most common sensitivity (504, 66.23%, Df 60.3%, Dp 59%), followed by an animal dander (302, 39.68%, cat epithelium 33.5%, dog epithelium 29.2%, horse epithelium 11.3%), cockroach (263, 34.56%), grass and cereal pollen (246, 32.33%), molds (240, 31.54%, *Alternaria alternata* 24.8%, *Aspergillus fumigatus* 11.8%, *Cladosporium herbarum*

13.4%), weed mixture (221, 29.04%), olive tree (212, 27.86%), and tree mixture (114, 14.98%). The frequency of sensitization to aeroallergens is shown in Figure 1.

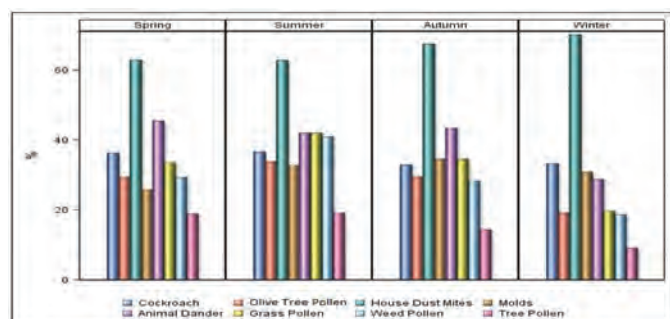
When the allergen sensitivities were examined according to allergic diseases, HDMs were the most common in all patient groups, followed by animal dander, and cockroach. A significant difference was determined between patients with and without allergic rhinitis, the sensitivity to grass cereal mixture, olea tree and weed mixture was found to be higher in the AR group ( $p<0.001$ ,  $p=0.031$ ,  $p=0.016$  respectively). There were no significant differences between these two groups in terms of other allergens.

When the patients with asthma and allergic rhinitis were compared to those with only asthma and only AR, sensitization to HDM and aspergillus was found to be higher ( $p<0.001$ ,  $p=0.033$  respectively).

When evaluated according to season, HDMs were the most common allergen in all seasons. In winter, animal dander ( $p=0.03$ ) and pollen sensitivity frequencies were lower ( $p<0.001$ ). The frequency of aeroallergens sensitization by season is shown in Figure 2.



**Figure 1.** Frequency of sensitization to aeroallergens among atopic children



**Figure 2.** Aeroallergen distribution by seasons

### Sex and Allergen Sensitization

AR was more common in boys ( $p=0.028$ ). Females showed higher test positivity rates for cats compared to males ( $p=0.008$ ). No significant difference was observed between the sexes with respect to the remaining allergens.

### Age and Allergen Sensitization

Patients were categorized into three age groups: 2-5 years (mean age  $4.07\pm 0.7$ , median 4.25 years), 5-10 years (mean age  $7.38\pm 1.43$ , median 7.37 years), and more than 10 years (mean age  $13.61\pm 2.28$ , median 13.4 years). Significant differences were determined between the age groups in AR and AS ( $p<0.001$ ) AR was lower in the 2-5 year group ( $p<0.001^{***}$ ) and AS was lower in the >10 year group (Table 1).

Sensitization to animal dander ( $p<0.001$ ), cockroach ( $p=0.016$ ), aspergillus ( $p=0.013$ ), claudosporium ( $p<0.001$ ), grass-cereal mix ( $p<0.001$ ), weed mix ( $p<0.001$ ), tree mix ( $p=0.002$ ), and olea tree ( $p<0.001$ ) showed an increasing trend with age. The sensitization rates were higher in the group aged more than 10 years compared to the 2-5 years and 5-10 year groups. The distribution of aeroallergens by the age group is shown in Figure 3.

### Aeroallergens Sensitivities According to Atopic Diseases

In patients with only AR, grass mix (40.4%), grass-cereal mix (40.4%), weed mix (31.27%), and olea tree (30.97%) sensitization rates were higher than in the AS and AS+AR groups ( $p<0.001$ ,  $p=0.003$ ,  $p=0.031$ , respectively).

In the AS+AR group HDMs (*D. pteronyssinus* 67.82%, *D. pharinaea* 68.82%) and aspergillus (15.29%) sensitization rates were higher than in the AS and AR only groups ( $p<0.001$ ,  $p=0.03$ , respectively).

In patients with only AD, HDMs, cockroach, animal dander and grass pollen sensitization were observed. The distribution of aeroallergens by allergic diseases is shown in Figure 4.

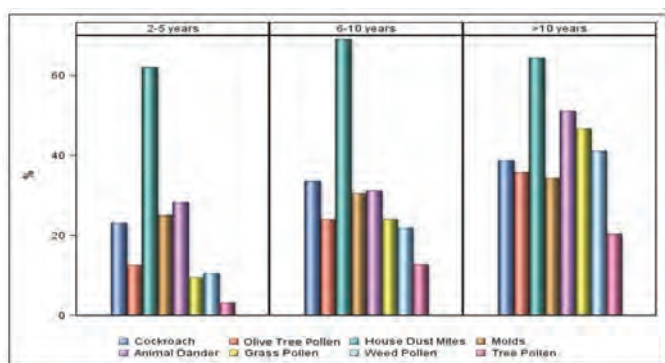
## DISCUSSION

Aeroallergens sensitization is increasing world-wide. The variability in aeroallergens sensitivity of children may differ not only between countries but also between cities in the same country with different climatic conditions (6). Climate change, pollution, altitude, and diverse human activities affect aeroallergens sensitivity. Identifying allergens is an important step in diagnosing allergic respiratory disease. Epidemiological studies show that the global distribution of aeroallergens, such as HDMs and pollen, varies geographically and seasonally. Pollen

**Table 1. Age group categorisation of patients**

	2-5 years		6-10 years		>10 years		p value
	n	%	n	%	n	%	
Total	95	12.48	328	43.10	338	44.42	
Boys	61	64.21	190	57.93	188	55.62	0.32
Girls	34	35.79	138	42.07	150	44.38	
AD	16	16.84	41	12.5	33	9.76	0.15
AR	73	76.84	286	87.2	320	94.67	<0.001***
AS	64	67.37	207	63.11	140	41.42	<0.001***
Polysensitisation	45	8.38	215	40.04	277	51.58	<0.001***
Monosensitisation	50	22.32	113	50.45	61	27.33	

AD: Atopic dermatitis, AR: Allergic rhinitis, AS: Asthma

**Figure 3.** Aeroallergen distribution by age groups

allergens are usually found in subtropical or temperate climates rather than tropical, and their surrounding concentrations vary throughout the year depending on the ecological season (10,11).

In our study, sensitivity to HDMs was the most common, followed by animal dander and cockroach. Other aeroallergens sensitivities were to molds and pollens. The sensitization rates to pollen were determined to be higher in the AR only group than in the AS and AS+AR groups.

In the AS+AR group, HDMs and aspergillus sensitization rates were higher than in the AS only and AR only groups.

In a study by Hazar Sayar (8), conducted in Alanya region in an other region of southwestern Turkey between 2017 and 2018, of children aged 2-18 years, the most common sensitivities were determined to be HDMs (76.1%), followed by fungal spores (51.8% *Alternaria alternata*, 41.7% *Cladosporium herbarum*), and grass and cereal pollen (39.8%). In another study by Basaran et al. (9) in the Mediterranean region covering the years 2014-2015, the most common sensitivity was to HDMs at 69% followed by tree pollen mixture at 54.9% and grass and cereal pollen mixture at 52.5%. Previous studies conducted in Turkey have determined HDMs to be a significant allergen. Harmançi et al. (12) reported house dust mite sensitivity of 46.3% in pre-school-age children in

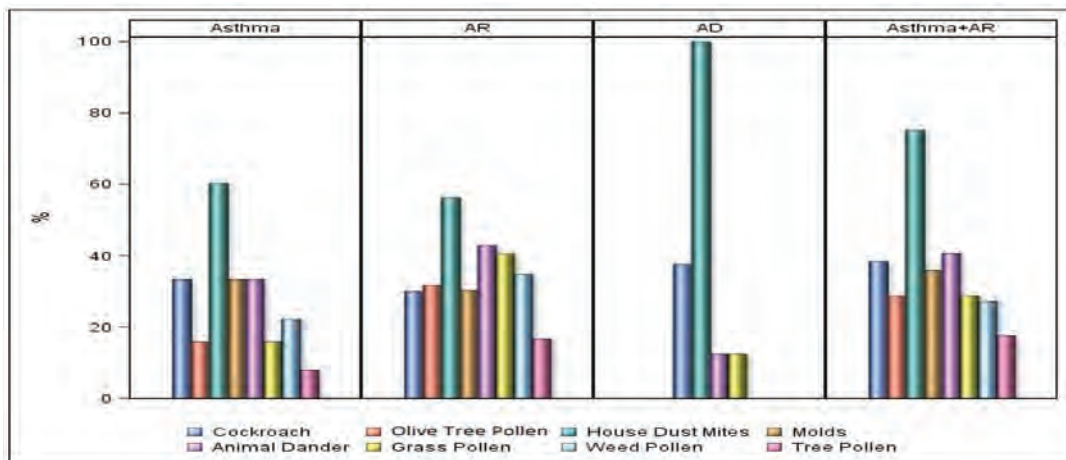
Ankara, Yazicioglu et al. (13) reported this rate as 52.1% in children aged 4-17 years in the Thrace region, and Şaşıhüseyinoğlu et al. (14) determined the most common allergen sensitivities to be Dp (73.8%) vs. Df (71.6%). Ozkaya et al. (15) compared two regions at different altitudes and reported that house dust mite sensitivity was greater in İstanbul at sea level than in Erzurum at high altitude (72.3% vs. 22.6%), and pollen sensitivity was higher in Erzurum. Thus, it was stated that the mite allergy is associated with high humidity and low altitude (15).

A previous study that included various regions of Turkey showed that the presence of mites was related to an increase in both mean temperature (>15 °C) and humidity (40%), as well as low altitude (<300 m) (16).

Several studies have shown that mite sensitivity is associated with an increased risk of rhinitis and asthma in both children and adults (17,18) and that exposure to HDMs, pollens, molds, and animal dander is a significant risk factor in the development of allergic diseases in children (19). Mite allergy is the most important and most common indoor allergen associated with airway sensitivity.

Turkey acts as a bridge between Asia and Europe, and is surrounded by sea on three sides. Geographical and climatic changes cause aeroallergens diversity and various aeroallergens sensitivities are observed.

Antalya is located in western Anatolia. According to the Köppen-Trewarta climate classification, Antalya is Cshk; scalding summers, cool winters, subtropical dry summer climate, Mediterranean climate (20). The average annual humidity is 65% and the average monthly relative humidity ranges from 58% in July to 70% in December. The temperature typically varies from 5 °C to 34 °C and is rarely below 1 °C or above 39 °C. The warm and humid climate provides an ideal environment for mites and cockroaches.



**Figure 4.** Aeroallergen distribution by allergic diseases

AR: Allergic rhinitis, AD: Atopic dermatitis

In this study, sensitization to HDMs is expected to be high due to regional geography with 60-70% humidity and the location at an altitude of 100 m above sea level.

Sensitization to pet allergens from domestic exposure is gradually increasing. As the rate of pet ownership increases, direct or indirect exposure to pets may also increase the rate of sensitization to pet allergens. Animal dander can also cause allergies in those without an animal at home, as animal danders sticky and airborne. As pet owners carry animal dander to public places on their clothes, it can be found in the air, even in public places where there are no animals present (21,22). Animals are the third leading cause of allergic asthma, after mites and pollen (23). In this study, animal dander was the second most common sensitivity. Cats and dogs can be found in almost every area of Antalya. Females showed higher test positivity rates for cats. It was thought that cat sensitivity was more common in females as females are more likely to own cats than males.

It is common for many patients to be sensitized to both cats and dogs (23) and 75% of pet-sensitized patients are 14 times more likely to be sensitized to other animals (24). In a study conducted in Korea, sensitization to cats was found to be a risk factor for sensitization to dogs, and vice versa (22). In the current study, 81.5% of patients with cat sensitivity also had dog sensitivity, and 71% of those with dog sensitivity also had cat sensitivity. Of the patients with horse sensitivity, 89.5% also had dog sensitivity and 90.7% had cat sensitivity. Structural similarities and/or homology between various dogs and cat allergens (such as albumin and lipocalin) explain the cross-reactivity between them and with other mammals (23,25).

Cockroach allergy has been identified as an important cause of respiratory allergic diseases and exposure to

cockroach may lead to exacerbations of asthma and/or allergic rhinitis in sensitized patients.

More than 20 different cockroach species have been identified in Turkey, of which *Blattella germanica* has been reported to be the most common (26). Cockroach allergen levels are correlated with the severity and increase in morbidity of asthma. Previous studies have reported that the cockroach allergy prevalence rate varies from 17- 58% of atopic allergies in the USA and 4-26% in Europe and 2.2-51.4% in Turkey in various studies of both children and adults (13,26-28). In a study of respiratory-allergic adults in İzmir, cockroach allergy was seen in 36.2% and sensitivity to cockroach allergens was determined to be more frequently associated with other indoor allergen sensitivities, especially dog, cat dander and mite sensitivity. This co-existence was attributed to the fact that patients might be simultaneously exposed and thus become sensitized to these allergens, and this co-sensitization with other indoor allergens might also contribute to the early development of asthma and a more severe course of the disease (29). Similarly, in the current study, indoor allergen sensitivities to mite, animal dander and cockroach were the three most common allergens. Cockroach-sensitive patients were also sensitized to mites at a rate of 89% and to animal dander at 48.3%. Cockroach sensitivity in the current study was 34.56% and 89% of cockroach-sensitive patients were also sensitive to HDMs. Previous studies have demonstrated that 70% of patients with a cockroach allergy were also sensitive to HDMs, suggesting cross-reactivity between the two allergens in both adults and children (26,30). The co-existence of cockroach and house dust mite allergen sensitivity is well known. Tropomyosin causes a cross-reaction between house dust mite allergen, cockroach allergen, parasites and shrimp allergens (31).

A previous study has shown that in addition to homes, kindergartens and schools are highly exposed to mite and



cockroach allergens, which may contribute to sensitization (32).

As cockroaches prefer to live in high temperatures and humid environments, there is increased exposure in seaside regions, which explains the higher frequencies of cockroach sensitivities among patients living in Antalya. Cockroach infestations are considerably higher in patients with a low socioeconomic level and poor housing conditions. Unfortunately, the socioeconomic status of the patients in this study could not be assessed. The eradication of cockroaches depends on meticulous attention to hygiene and regular use of insecticides.

Atopy is more common in the male sex (33). In this study 57.69% of the patients were male and 42.31% were female, and AR was more common in boys, which was consistent with the literature.

Aspergillus sensitization has been reported in previous adult and pediatric studies to be associated with poorly controlled and severe asthma (34,35). In this study, aspergillus sensitivity was found to be high in patients with asthma only, but since asthma control was not evaluated in this study, the relationship with poorly controlled or severe asthma could not be evaluated.

When we examined the aeroallergens sensitivities according to age, it was observed that the house dust mite allergy was observed most frequently and polysensitization increased with age.

## CONCLUSION

The results of this study detected environmental aeroallergens sensitivity and common allergens in our region. Indoor allergen sensitivity was common in this study, which was attributed to rising temperatures and humidity recently in Antalya. Global climate change, seasonal changes, and aeroallergens concentrations are expected to influence the future prevalence, severity, and manifestation of allergic diseases. Regional studies can provide important clinical information about the nature and course of allergic diseases and future treatment options.

## Ethics

**Ethics Committee Approval:** It was approved by the Local Ethics Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (2020, 10/16).

**Informed Consent:** Informed consent was obtained from all the patients.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: Ş.K., S.F., Design: Ş.K., S.F., Data Collection or Processing: Ş.K., Analysis or Interpretation: Ş.K., S.F., Literature Search: Ş.K., S.F., Writing: Ş.K., S.F.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Coexistence of Intramuscular Hematoma in Patients with a Diagnosis of COVID-19

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## Abstract

**Objective:** The current study emphasizes that intramuscular hemorrhage should be considered in cases where low-molecular-weight heparin is applied to prevent and treat hypercoagulability in coronavirus disease-2019 (COVID-19), and these cases should be followed closely because spontaneous bleeding complications may also occur in COVID-19.

**Methods:** The current study included 24 patients who were hospitalized with a diagnosis of COVID-19 and who had intramuscular bleeding during their follow-up. Data such as gender, age, diabetes, hypertension, cancer history, previous intra-abdominal surgery, coronary artery disease, presence of additional disease such as kidney failure, drugs used before and after hospitalization, and patients' need for intensive care, and the need for intubation and blood replacement were recorded for all patients.

**Results:** Of the patients, 16 (66.7%) were male, 8 (33.3%) were female, and the mean age was 71.9 (47-87) years. Comorbidities were present in 18 of the patients. It was seen in radiology reports that 54.2% of intramuscular bleeding developed within the psoas muscle in the retroperitoneum. In 21 (87.5%) patients, erythrocyte replacement therapy was performed in line with the clinical findings because of bleeding. The number of patients whose treatment required intensive care was 14 (58.3%) and 6 (25%) patients had to be intubated. Mortality was seen in 9 (37.5%) patients. The presence of comorbidity, international normalized ratio value, high pressure oxygen therapy, the need for intensive care and the need for intubation showed statistically significant differences in the development of mortality.

**Conclusion:** To reduce mortality and morbidity due to hypercoagulability that may develop after COVID-19 infection, more studies on how, at what doses and when anticoagulation should be given and the preparation of guidelines for this will be beneficial in treatment management. It is thought that cases with intramuscular bleeding should be observed closely, supportive treatment should be applied promptly, and surgical option should be considered.

**Keywords:** COVID-19, retroperitoneal hematoma, enoxaparin

## INTRODUCTION

Coronavirus disease-2019 (COVID-19) turned into a pandemic that affected the entire world in 2020 after the first case was reported in Wuhan, China (1). In addition to clinical findings such as muscle pain, fatigue, cough, and fever, shortness of breath, pneumonia, and even acute respiratory distress syndrome (ARDS), which greatly affects mortality, can be seen among the symptoms of the disease (2). Although almost 2 years have passed since the initiation of the pandemic, different

clinical symptoms, and complications can be seen in COVID-19 patients.

Microthrombosis is one of the most severe complications of COVID-19 and affects predominantly respiratory system. Because of these microthrombosis, an increased incidence of pulmonary thromboembolism and cerebrovascular disease was observed (3). Inflammation, endothelial dysfunction, and related thrombosis are also observed in patients with vascular involvement after COVID-19 (2). Especially since pulmonary thromboembolism is a



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**Cite this article as:** Atay M, Gemici E. Coexistence of Intramuscular Hematoma in Patients with a Diagnosis of COVID-19. Eur Arch Med Res 2022;38(4):288-294

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 08.09.2021

**Accepted:** 04.04.2022

complication that increases mortality, many studies recommend the use of heparin, low-molecular-weight heparin (LWMH), and other anticoagulants in the treatment (4).

LWMH is routinely used in our clinical for the prevention and treatment of hypercoagulopathy in COVID-19 patients. Prophylactic dose anticoagulation should be used in hospitalized COVID-19 patients by monitoring bleeding in American Society of Hematology guidelines (5).

Intramuscular hemorrhage was observed in 24 patients who were hospitalized and followed up by us due to COVID-19. The current study emphasizes that intramuscular hemorrhage should be considered in cases where LWMH is applied to prevent and treat hypercoagulability in COVID-19, and these cases should be followed closely because spontaneous bleeding complications may also occur in COVID-19.

## METHODS

A total of 24 patients who were hospitalized with the diagnosis of COVID-19 in Bahcelievler State Hospital and University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital between March 2020 and May 2021 and who had intramuscular bleeding during their follow-up were included in the current study. Patient information, laboratory results, computed tomography (CT) reports and clinical course were retrospectively reviewed. Data such as gender, age, diabetes, hypertension, cancer history, previous intra-abdominal surgery, coronary artery disease (CAD), presence of additional disease such as kidney failure, drugs used before and after hospitalization, and patients' need for intensive care, and the need for intubation and blood replacement were recorded for all patients.

Patients with any blood disease, a history of previous intra-abdominal surgery and femoral vascular catheterization, and a three-month history of trauma were excluded from the study.

This study was designed in accordance with the principles of the Declaration of Helsinki. Approval received from the Ministry of Health COVID-19 Scientific Research Oversight Committee (2021-05-25T08\_36\_48).

### Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 24.0 program was used in the analysis of the variables. Evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as the independent samples t-test was used for comparisons of normally distributed groups, while Mann-Whitney U test was

used for comparisons of non-normally distributed groups. The Pearson chi-square test was used in the analysis of qualitative data. The multivariate regression analysis was used to determine the effect levels. Significance was evaluated at  $p < 0.01$  and  $p < 0.05$  levels.

## RESULTS

The data of 24 patients who were hospitalized with the diagnosis of COVID-19 and had intramuscular bleeding during their follow-up were analyzed. The demographic data showed that 16 (66.7%) patients were male and 8 (33.3%) were female. The mean age was  $71.96 \pm 13$  (47-87) years. Comorbidities were present in 18 of the patients. When the diseases were investigated, it was seen that hypertension was the first, followed by diabetes mellitus, CAD, and chronic kidney failure (Table 1). During the examination of the hospitalization files, it was seen that lung involvement was classified in the severe category in 41% of the patients. Radiology reports showed that 54.2% of intramuscular bleeding developed in the psoas muscle in the retroperitoneum. Erythrocyte replacement therapy was performed in 21 (87.5%) patients, in line with the clinical findings because of bleeding. The number of patients whose treatment required intensive care was 14 (58.3%) and 6 (25%) patients had to be intubated. Mortality developed in 9 (37.5%) patients (Table 1). The mean hospital stay of all patients was 13.8 (3-31) days. Radiological examinations showed that intramuscular hemorrhages also occurred on average on the fifth day of hospitalization. The mean hemoglobin (Hgb) value of the patients was measured as 8.6 (g/dL), mean leukocyte count as  $13.7 (\times 10^3/\text{mL})$ , mean platelet count as  $191.25 (\times 10^3/\text{mL})$ , mean international normalized ratio (INR) value as 1.31, mean prothrombin time (PT) 1.84 (sec), mean activated partial thromboplastin time (aPTT) as 38.5 (sec), mean fibrinogen concentration as 463.17 (mg/dL), and mean lactate dehydrogenase level (LDH) as 455 (U/L). It was seen that oxygen support was provided to all patients and they received this treatment on an average of 10 liters. The mean intramuscular hemorrhage size was 84 mm and an average of 4 units of erythrocyte replacement was applied to the patients (Table 1).

The patients who had intramuscular bleeding were divided into two groups according to their mortality status and the factor causing mortality was questioned. When the group discharged from the hospital with recovery and the group that had mortality were examined considering the parameters reported above, there was no statistical difference between the two groups in terms of gender distribution, COVID involvement degree, hematoma location, and erythrocyte replacement status ( $p > 0.05$ ). However, the presence of comorbidity, the need for intensive care, and the

need for intubation showed statistically significant differences ( $p=0.028$ ,  $p=0.019$ ,  $p=0.001$ ,  $p<0.05$ , respectively) (Table 2).

		n	%
Gender n (%)	Male	16	66.7
	Female	8	33.3
Comorbidity n (%)	Absent	6	25.0
	Present	18	75.0
HT		14	77.8
DM		4	22.2
COPD		3	16.7
KAH		4	22.2
CVO		3	16.7
CRF		4	22.2
COVID involvement rate n (%)	Mild	5	20.8
	Medium	9	37.5
	Severe	10	41.7
In-hospital mortality n (%)	No	15	62.5
	Yes	9	37.5
ICU admission n (%)	Absent	10	41.7
	Present	14	58.3
Intubation n (%)	Absent	18	75.0
	Present	6	25.0
Place of hematoma n (%)	Rectus muscle	11	45.8
	Retroperitoneum	13	54.2
Patients with RBC transfusion n (%)	No	3	12.5
	Yes	21	87.5
		Mean $\pm$ SD	
Age (year)		71.96 $\pm$ 13	
Day when the bleeding occurred (days)		5.04 $\pm$ 3.69	
Length of hospital stay (days)		13.83 $\pm$ 3.69	
Hemoglobin (g/dL)		8.69 $\pm$ 7.17	
INR levels		1.31 $\pm$ 0.42	
Prothrombin time, (%)		1.84 $\pm$ 2.6	
Activated partial thromboplastin time, (sec)		38.5 $\pm$ 18.2	
Platelet ( $\times 10^3$ /mL)		191.25 $\pm$ 96.58	
Leucocyte ( $\times 10^3$ /mL)		13.73 $\pm$ 11.03	
Lactate dehydrogenase (U/L)		455 $\pm$ 169.12	
Fibrinogen concentration (mg/dL)		463.17 $\pm$ 152.75	
Pressurized oxygen liter (L)		10.88 $\pm$ 8.05	
Hematoma diameter (mm)		84.54 $\pm$ 34.7	
Amount of replacement (unit)		4.33 $\pm$ 2.71	
HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive lung disease, CVO: Cerebrovascular occlusion, CRF: Chronic renal failure, ICU: Intensive care unit, RBC: Red blood cell, COVID: Coronavirus disease, SD: Standard deviation			

The data of both groups, such as mean age, day of bleeding, length of hospital stay, Hgb value, platelet count, PT value, aPTT value, LDH value, fibrinogen concentration, hematoma diameter, and amount of erythrocyte replacement did not show any statistically significant difference ( $p>0.05$ ). However, INR value ( $p=0.014$ ;  $p<0.05$ ) and leukocyte values ( $p=0.008$ ;  $p<0.05$ ) differed statistically, and these values were higher in the mortality group. Similarly, it was observed that pressure oxygen therapy was given at a higher amount in the mortality group, and this showed a statistically significant difference ( $p=0.001$ ;  $p<0.01$ ) (Table 3).

Because of the comparison of the groups, factors associated with mortality were determined. Multivariate analysis was performed on the variables to determine which of these variables made the strongest difference. Intubation requirement and leukocyte value were found to be significant in the model because of multivariate analyses ( $p<0.01$ ) (Table 4).

## DISCUSSION

COVID-19 can cause thrombosis in both small and large vessels due to microthrombi. The incidence of deep vein thrombosis in patients diagnosed with COVID-19 and undergoing autopsy is almost 50% (3). Additionally, complement-mediated microvascular damage and thrombosis were observed in the autopsies of patients who developed ARDS after COVID-19 (6). In their autopsy study conducted in patients who developed ARDS after COVID-19 and influenza, Ackermann et al. (7), reported that the development of capillary microthrombus was nine times higher in the COVID-19 group. In other studies, it was reported that many cases develop hypercoagulopathy after COVID-19 (2). In a study conducted in an intensive care unit, venous thromboembolism was found in many patients who developed ARDS after COVID-19 and used anticoagulants (2,8). As seen in the literature, in patients followed up for COVID-19, respiratory failure is caused by microthrombus (9,10). This hypercoagulable state, which is thought to be triggered by proinflammatory cytokines, can cause microvascular thrombi, multi-organ failure and death (9,11). In a study, 449 patients with a diagnosis of COVID-19 were examined and heparin did not have a significant effect on the 28-day mortality. Again, in the same study, mortality was found to be significantly lower after heparin use in the group with D-dimer levels more than 6 times the normal value (12). Therefore, the patients followed up in this study had been using LWMH since hospitalization.

Although the World Health Organization and the American Society of Hematology recommend the use of anticoagulation

		Ex		Discharged		<sup>a</sup> p
		n	%	n	%	
Gender	Male	5	55.6	11	73.3	0.371
	Female	4	44.4	4	26.7	
Comorbidity	Absent	0	0.0	6	40.0	0.028*
	Present	9	100.0	9	60.0	
COVID involvement rate	Mild	3	33.3	2	13.3	0.367
	Medium	2	22.2	7	46.7	
	Severe	4	44.4	6	40.0	
ICU admission	Absent	1	11.1	9	60.0	0.019*
	Present	8	88.9	6	40.0	
Intubation	Absent	3	33.3	15	100.0	0.001**
	Present	6	66.7	0	0.0	
Place of hematoma	Rectus muscle	3	33.3	8	53.3	0.341
	Retroperitoneum	6	66.7	7	46.7	
Patients with RBC transfusion n (%)	No	1	11.1	2	13.3	0.871
	Yes	8	88.9	13	86.7	

<sup>a</sup>Pearson chi-square, \*p<0.05, \*\*p<0.01, COVID: Coronavirus disease, RBC: Red blood cell, ICU: Intensive care unit

	Ex		Discharged		<sup>b</sup> p
	Mean ± SD	Min-max (median)	Mean ± SD	Min-max (median)	
Age	76.22±13.48	47-87 (81)	69.4±12.46	49-86 (75)	0.107
Day when the bleeding occurred	5.11±3.06	2-11 (5)	5±4.12	1-18 (5)	0.696
Length of hospital stay (days)	11.67±4.3	3-17 (12)	15.13±8.32	3-31 (14)	0.437
Hemoglobin (g/dL)	8.14±1.81	6.4-11.9 (7.4)	9.02±1.66	5.3-12.1 (9.3)	0.083
INR levels	1.49±0.4	1-2.4 (1.39)	1.19±0.41	0.8-2.4 (1.1)	0.014*
Prothrombin time, (%)	1.69±0.4	1-2.4 (1.39)	2.05±3.3	0.8-13.9 (1.1)	0.078
Activated partial thromboplastin time, (sec)	51.28±23.83	22.4-86.8 (42)	40.84±7.18	16.9-45.6 (30.5)	0.219
Platelet (×10 <sup>3</sup> mL)	172.56±109.62	44-372 (155)	202.47±89.98	98-382 (171)	0.325
Leucocyte (×10 <sup>3</sup> mL)	20.78±15.25	10-58 (16)	9.49±3.98	4-18 (8)	0.008**
Lactate dehydrogenase (U/L)	515.56±183.3	189-787 (507)	418.67±154.97	234-893 (391)	0.101
Fibrinogen concentration (mg/dL)	490.67±171.17	120-703 (538)	446.67±144.26	261-740 (402)	0.270
Pressurized oxygen liters	18.89±7.08	6-30 (20)	6.07±3.43	2-15 (4)	0.001**
Hematoma diameter (mm)	85.56±29.89	27-125 (69)	95.93±33.12	40-160 (100)	0.739
Replacement amount (U)	6±3.7	1-12 (6)	3.31±1.11	2-6 (3)	0.058

<sup>b</sup>Mann-Whitney U Test, \*p<0.05, \*\*p<0.01, INR: International normalized ratio, SD: Standard deviation

with LWMH in hospitalized COVID-19 patients, there are no guidelines describing dosages and indications (1,9). In a study conducted in China, the use of fractionated heparin was recommended in the treatment because it can be controlled with protamine and is short-lived. However, some researchers reported that this requires frequent injections and may spread the infection (1).

Patients under anticoagulation may encounter a clinical picture ranging from simple hemorrhages to life-threatening retroperitoneal hemorrhages if not followed carefully. Bleeding can also occur spontaneously without anticoagulant drugs. These can often develop due to severe coughing, pregnancy, and trauma. Especially, the superior epigastric artery and its branches passing through the rectus muscles can be injured after sudden and high-intensity contractions in the muscles (13).



	Multivariate p value	Odds ratio	95% CI for EXP (B)	
			Lower	Upper
<b>Comorbidity</b>	0.346	0.125	-0.164	0.442
<b>ICU admission</b>	0.199	0.181	-0.103	0.459
<b>Intubation</b>	<b>0.005</b>	<b>0.684</b>	<b>0.266</b>	<b>1.262</b>
<b>INR</b>	0.794	0.031	-0.254	0.327
<b>Leucocyte</b>	<b>0.009</b>	<b>0.558</b>	<b>0.007</b>	<b>0.043</b>
<b>Pressurized oxygen liters</b>	0.550	-0.168	-0.046	0.025

ICU: Intensive care unit, INR: International normalized ratio, CI: Confidence interval

Retroperitoneal bleeding is seen, especially around the psoas muscle, and the hematoma can grow up to 10 times that of the psoas muscle (14,15). The incidence may also increase after heparin administration. Intramuscular hematoma can be seen after LWMH application, particularly in elderly patients, even if there is no underlying disease (2). However, it has been stated in many studies that COVID-19 is also a factor that develops spontaneous muscle hematoma (2). In the literature, studies have stated that hematochezia, subarachnoid, and intracerebral hemorrhage, petechiae and purpura are seen after COVID-19 (2). In one study, a large intracerebral hemorrhage was detected by CT in a 79-year-old patient who was followed up for COVID-19 and did not have hypertension and did not receive anticoagulant therapy (16). Terzi et al. (17), on the other hand, reported a case of intramural hematoma seen after COVID-19 and emphasized that it can cause vascular damage with inflammation, microangiopathy, and thrombosis in the vascular system in COVID-19 patients in the same study. Rogani et al. (2), similarly, stated that not only hypercoagulability is observed in COVID-19, but also bleeding may develop. In this study, bleeding was detected in 11 patients (45.8%) in the rectus muscle and in 13 patients (54.2%) in the retroperitoneal region. No underlying cause for bleeding was found in these patients. However, bleeding in the mortality group was in the rectus muscle in 3 patients (33.3%) and in the retroperitoneal area in 6 patients (66.7%). In this study, there was no statistically significant relationship between the site of hematoma and mortality ( $p=0.347$ ).

In another case, hematoma in the neck and upper chest was reported after prophylactic LWMH use (18). In another study, 4 patients who were treated with LWMH in post-COVID-19 treatment and who developed hematomas in different regions were treated with vascular coil embolization that caused bleeding. In the study, it was evaluated that trauma may have bled 2 patients, while no cause was found in the other two patients (19). In a case study by Javid et al. (3), we presented

a patient who was followed up with the diagnosis of COVID-19 and developed spontaneous retroperitoneal hematoma and had no known disease other than hypertension and diabetes before. Since D-dimer was higher than normal, 5000 units of intravenous heparin was given to the patient every 6 h. After 2 days, the patient started to have right flank pain and a large bleeding area was observed around the psoas muscle in the contrast-enhanced CT. After heparin was discontinued, the patient's hematoma regressed. As a result, they recommended careful monitoring of Hgb levels in patients who received heparin at the therapeutic dose (3). In this study, 18 patients (75%) had an additional disease. The mean Hgb level was found to be 8.69. While gender, age, degree of COVID involvement, the location of hematoma, Hgb, aPTT and platelet level, and amount of blood transfusion were not statistically significant in terms of mortality, the presence of additional disease and high leukocyte level were found to be factors affecting mortality ( $p=0.028$ ,  $p=0.008$ ). Contrary to the current study, in the study by Lippi et al. (20), low leukocyte levels were found to be significant in terms of mortality. They also stated that low platelet count was also associated with mortality (20). In the study by Canoglu and Saylan (1) similar to the current study, the platelet level was not found to be significant in terms of mortality. However, in the study by Canoglu and Saylan (1), INR, and aPTT levels were significant in terms of mortality. Although INR, aPTT and platelet levels are not significant in the current study, low platelet levels will lead to continued bleeding ( $p=0.014$ ,  $p=0.219$ ,  $p=0.325$ ). It is considered that this will increase mortality later on.

Conti et al. (21) reported two psoa hematomas that developed pneumonia due to COVID-19 and were supported by a continuous positive airway pressure (CPAP) mask. LWMH was used in two patients and LWMH was administered at the therapeutic dose in one patient because of underlying DVT. Embolization under angiography was used as a treatment method in both patients. It was emphasized that the use of CPAP and cough symptoms may increase intra-abdominal bleeding (21). In this study, an average of 10.88 liters of pressurized oxygen was administered to all patients, and a statistically significant difference was found between the groups in terms of mortality ( $p=0.001$ ). Additionally, hospitalization in the intensive care unit and intubation of the patients were found to be statistically significantly correlated ( $p=0.019$ ,  $p=0.001$ ).

Intramuscular bleeding may present with hypotension, low Hgb, and abdominal pain. CT is useful for diagnosing (9). In this study, hematoma was determined by CT taken after hospitalization due to COVID-19 and CT images taken after low hemogram in the follow-ups. Hematoma localization and hematoma diameter were followed. The first recommendation in treatment is the

discontinuation of the anticoagulant drug, fluid replacement and support of the patient's blood values. In the case of active bleeding, endovascular and surgical methods can be applied (2,9). In the patient group in this study, supportive treatment was applied to the patients who had laboratory and clinical follow-ups. Mean Hgb levels were 8.69. hematoma diameter was measured to 84.54 mm on average. Blood transfusion was performed in 21 patients (87.5%). An average of 4.33 units of erythrocyte suspension was applied. Hgb level, mean hematoma diameter, and blood transfusion were not among the factors affecting mortality. Multivariate analysis was performed for comorbid disease, hospitalization in the intensive care unit, intubation, INR level, leukocyte level and pressurized oxygen liter, which are among the factors affecting mortality. In patients who developed intramuscular bleeding after COVID-19, the factors that most affected mortality was found to be high leukocyte levels and intubation ( $p=0.009$ ,  $p=0.005$ ).

## CONCLUSION

The COVID-19 pandemic has caused serious mortality and morbidity in our country and has become a major health problem. Hypercoagulable events such as proinflammatory processes and subsequent D-dimer increase are quite common in COVID-19. Hemorrhagic problems that may develop after hypercoagulability are not fully known. However, intramuscular bleeding is observed after the use of high-dose heparin for treating COVID-19. Therefore, to reduce mortality and morbidity, more studies on how, at what doses and when anticoagulation should be given, and the preparation of guidelines will be beneficial in the management of treatment. In conclusion, it is evaluated that cases with intramuscular bleeding should be kept under close observation, supportive treatment should be applied promptly, and a surgical option should be considered.

## Ethics

**Ethics Committee Approval:** This study was designed in accordance with the principles of the Declaration of Helsinki. Approval received from the Ministry of Health COVID-19 Scientific Research Oversight Committee (2021-05-25T08\_36\_48).

## Informed Consent:

**Peer-review:** Externally and internally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: M.A., E.G., Concept: M.A., E.G., Design: M.A., E.G., Data Collection or Processing: M.A., E.G., Analysis or Interpretation: M.A., E.G., Literature Search: M.A., Writing: M.A., E.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Histopathological Analysis of Nevi Excisions in Our Clinic

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## Abstract

**Objective:** Nevi are the most common benign lesions on the skin. Nevus excisions are performed to exclude the malignancies and for cosmetic reasons. The most reliable approach is excision and pathological examination to exclude malignant transformation for the nevi that have irregular borders, changing color, and a recent growing. The preliminary diagnoses, localizations and pathologic results after the excisional biopsies were presented in this study.

**Methods:** The study is a retrospective case series including 1.576 excised nevi in 1.382 patients between 2016 and 2019. The patients were evaluated retrospectively in terms of the pathologic results and demographic data such as age, gender and nevus localization. The clinical preliminary diagnoses of all excised lesions were listed as nevi. Malignant and benign results were compared statistically.

**Results:** The patients included in the study were between the ages of 5-85. Twenty different types of pigmented skin lesions were identified. The mean age of patients with malignant results was 51.1, while the mean age of patients with benign results was 34.4 ( $p=0.054$ ). The most common nevus locations were head and neck (76.98%), followed by trunk (16.04%), upper extremity (4.39%), and lower extremity (2.57%). When the pathological diagnoses and frequencies of the excised nevi were examined; intradermal compound or blue nevi were observed in 45.4% of all patients.

**Conclusion:** Melanocytic nevi are mostly benign and excision is mostly performed for cosmetic purposes. However, since there is a possibility of malignant transformation in atypical nevi; these should be excised to rule out malignancy.

**Keywords:** Biopsy, excision, nevi

## INTRODUCTION

Skin consists of the epidermis, dermis and subcutaneous tissue. Cell lines settled in the skin include keratinocytes, hair follicles and sebaceous glands, sweat glands, and smooth muscle cells (1). The term “nevus” does not have a specific definition, as many nevi are either congenital or acquired. Others are localized in different layers of the skin. Moreover, proliferating cell types are different among nevi. Happle (2) defined nevi as “Lesions that have genetic mosaicism, well-defined borders and which are located on the skin or mucosa for a long time”, except that melanocytic nevi do not have neoplastic potency.

The principal risk with a nevus is the possibility for malignant transformation and the risk is higher in the congenital nevi. This risk increases in relation to the size with the highest for nevi dimensions exceeding 20 cm (3,4). In acquired nevi, the malignant transformation possibility depends on the number of nevi or atypical structure of the nevus (5). In an acquired nevus, suspicious clinical properties for a possible malignant transformation include asymmetry, border irregularity, color differences, a diameter exceeding 6 millimeters, and evolving appearance which are universally abbreviated as ABCDE (6).

For nevi, the aim of excisional biopsies does not only include exclusion of possible melanomas, but also include cosmetic



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**Received:** 14.04.2022  
**Accepted:** 07.09.2022

**Cite this article as:** Aysal BK, Çolak Ö, Taşkın S, Gürel ZÖ, Yasak Par T, Üşçetin İ. Histopathological Analysis of Nevi Excisions in Our Clinic. Eur Arch Med Res 2022;38(4):295-298

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reasons. Many nevi are removed for cosmetic reasons (7), and this trend increases over time (8). Clinical approach to a nevus mainly depends on total excision, however other available methods include punch or shave excisions and abrasive techniques (9-11).

In this study, a large series of patients were presented in whom total excisional biopsies were performed in a plastic surgery department of a tertiary health center.

## METHODS

### Patients

This is a retrospective clinical study including patients with nevi. Between 2016 and 2019, 1382 patients were operated and 1576 nevi were excised. Patient age ranged from 5 to 85 (mean age, 34.59). All nevi were located on the skin and removed by total excision under local anesthesia in plastic surgery outpatient operating room. The preliminary diagnosis included nevus in all the patients, compared to malignant melanoma in 45 of the patients. The resultant defects were repaired by primary closure. All of the removed nevi were sent for pathologic examination. No major complications were encountered in the follow-up period. Minor complications included local infection in 27 surgical sites (1.7%) and wound dehiscence in 37 surgical sites (2.3%). All minor complications were managed with conservative methods. Patients were evaluated for demographic data, as well as localization and pathologic results of the nevi.

For the study, University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, Ethics Committee approval was obtained (date: 21.03.2022, no: 76).

### Statistical Analysis

The results with the basal cell carcinoma (BCC) and the malignant melanoma were accepted as malignant and remaining results were accepted as benign. The relationship between the malignancy and age was studied. The software SPSS (Statistical Package for Social Sciences for Windows 22.0) was used to evaluate data statistically. Values were compared using the Student t-test. Outcomes were assessed at 95% confidence interval and 5% significance level. The p values below 0.05 were accepted as significant.

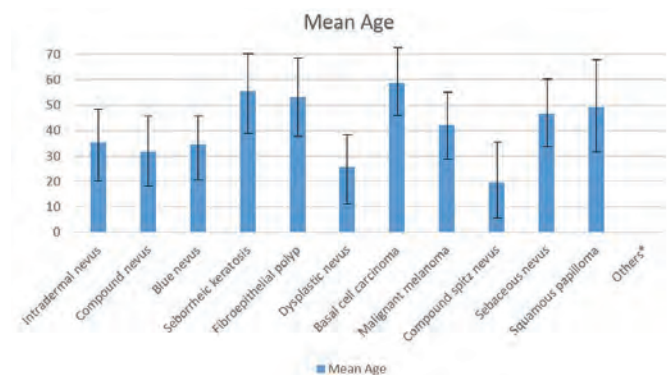
## RESULTS

Out of 1.576 masses, 27 were malignant (1.71%) including BCC and malignant melanoma. The mean age for malignant and benign results were 51.1 and 34.4 respectively. The malignant results were more common in older population as expected, however this result was not statistically significant ( $p=0.054$ ).

Patient age ranged from 5 to 85, where predominance of the patients was enrolled between 20 and 50 years of age (71.07%) (Figure 1). In the included patients, the head and neck were the most common anatomic site where 76.96% of the nevi were localized in this region after trunk (16.04%), upper extremity (4.39%) and lower extremity (2.57%). The pathologic examination results showed that the vast majority of the masses were intradermal and compound nevi with 50.44% and 38.44% of all cases, respectively. There were 20 different types of pathologic diagnoses. The diagnoses and mean age distribution are outlined in Table 1 and Figure 2.

## DISCUSSION

Our hospital is a very busy tertiary healthcare center located in Istanbul. Patients coming from different socio-cultural and socio-economic groups are admitted to our center. As a



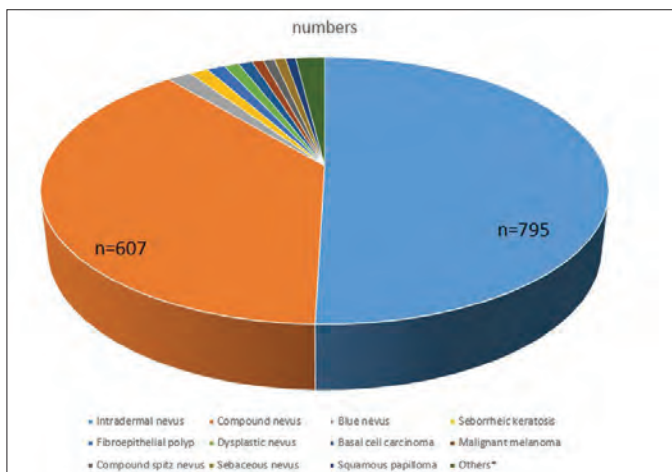
**Figure 1.** Mean ages of the included patients among pathologic results

**Table 1. The pathologic diagnoses and age distribution**

Pathologic diagnoses	Total number of samples (percentage)	Mean age of the group
Intradermal nevus	795 (50.44%)	35.2
Compound nevus	607 (38.44%)	31.8
Blue nevus	26 (1.64%)	34.8
Seborrheic keratosis	20 (1.26%)	55.6
Fibroepithelial polyp	19 (1.20%)	53.2
Dysplastic nevus	16 (1.01%)	25.6
Basal cell carcinoma	15 (0.94%)	58.6
Malignant melanoma	12 (0.75%)	42.2
Compound spitz nevus	12 (0.75%)	19.5
Sebaceous nevus	12 (0.75%)	46.6
Squamous papilloma	11 (0.75%)	49.4
Others*	31 (1.96%)	-

\*Others include dermatofibroma (0.50%), trichilemmal cyst (0.44%), verruca vulgaris (0.37%), capillary hemangioma (0.25%), keratoacanthoma (0.12%), syringoma (0.06%), fibrolipoma (0.06%), inflammatory linear verrucous epidermal nevus (0.06%), solar lentigo (0.06%)





**Figure 2.** Distribution of the pathologic results

result, the plastic surgery department has a high patient flow from outpatient admissions and from other departments such as dermatology. All the suspected skin lesions were sent for consultation to the plastic surgery department for excisional biopsy. When the demographic data and number of the included patients were checked, a homogenous distribution was revealed among all age groups including the pediatric and the elderly group. Size and content of the sample increase the safety of the study and lead to reliable results.

In the presented study 1.71% of the included nevi were non-benign lesions. The mean age with non-benign lesions is higher than the mean age with benign lesions, although this was not significant statistically ( $p=0.054$ ). This may be connected to the fact that malignant melanoma can be seen in young adults, or middle aged people as well. Of the included lesions, 0.75% of the nevi were malignant melanoma. This is, in number, 8.6 per thousand patients and 286 per 100.000 person-years. In studies conducted on a population-based health database, incidence of malignant melanoma per 100.000 person-years changed between 42 and 256 in the population (12-15). Our results are similar to these results. As one of the common malignancies of both genders (14,16), the incidence of malignant melanomas in 2004 was 7.7 and 13.7 per 100.000 people in males and females, respectively (17). This frequency explains the importance of the excisional biopsy for the suspected lesions. In the presented study, 45 of 1.576 patients had preliminary diagnoses of malignant melanoma. Of those, 12 had malignant melanomas and 16 had dysplastic nevi. All the lesions, which were resulted as malignant melanomas, had had macroscopic changes as summarized with before-mentioned ABCDE. Twenty of the lesions, preliminary diagnoses of which had been malignant melanoma, had dimensions exceeding 6 millimeters. This situation proves the fact that clinical suspicion for malignant melanoma is crucial.

BCC and squamous cell carcinomas (SCC) comprise the vast majority of skin malignancies. When combined, they are so common in number that their incidence exceeds 3 million in the United States and is more than all other cancers together (18,19). As a general rule, ratios of incidences of BCC, SCC, and malignant melanoma are 40, 10 and 1 respectively (20). In our study, more than half of the malignancies were melanoma, and no SCCs were encountered. However, SCCs are usually clinically well recognized lesions and as all included biopsies had preliminary diagnoses of nevi, no SCCs were encountered. Although BCCs usually have various clinical appearances, all superficially and non-superficially localized subtypes may have pigmented components (21-23). Fifteen of the lesions, preliminary diagnoses of which had been nevi, resulted in BCCs after pathologic examinations. Nine out of these 15 BCCs had had some macroscopic differences compared to regular nevi, including border irregularities, increased lengths and ulcerations.

The trunk is the most common localization for the malignant melanomas (24), however, nearly 77% of the lesions included in this study were localized in the head and neck region. This situation depends on the facts that many lesions were removed with cosmetic reasons and aesthetic concerns usually foreshadowed medical concerns in the head and neck. As Skaggs and Coldiron (8) stated, biopsy over cancer treatment ratio increased from 1.1 to 2.1 between 1993 and 2016. They stressed that biopsy numbers increased by 153%, whereas cancer treatments for skin tumors increased by only 39%. These ratios show that biopsies for cosmetic reasons have significantly increased in the last three decades. As BCCs are usually located in the head and neck region (25,26), their ratios cannot be used to reveal the distribution without bias. There are 12 malignant melanomas and 16 dysplastic nevi patients in our study, and only 29.16% of these were localized in the head and neck region (16.66% malignant melanoma and 12.5% dysplastic nevi, respectively). This shows that the main purpose for head and neck nevi removals are cosmetic reasons.

### Study Limitations

The presented study included a large patient sample. The results from 1.576 nevi can be accepted as reliable. One possible limitation of the study was its retrospective design. As distribution of the pathologic results would not change according to retrospectivity, prospective studies should be conducted to reveal the exact relationship between the preliminary and novel diagnoses.

## CONCLUSION

The nevi can be removed under local anesthesia with low complication rates. Complications can be managed by conservative techniques. The malignant and dysplastic lesions comprise a minor group among excision patients and there is no connection between aging and malignant results for skin nevi biopsies, however clinical features including asymmetry, border irregularities, color and diameter changes, evolving lesions and ulcerations should be considered carefully to reveal possibility of the malignant results. The skin biopsies are usually performed for cosmetic reasons in the head and neck region.

## ACKNOWLEDGEMENTS

We would like to thank Associate Professor Dr. Özben Yalçın for her great help in pathologic examinations.

## Ethics

**Ethics Committee Approval:** For the study, University of Health Sciences Turkey, Prof. Dr. Cemil Tascioğlu City Hospital, Ethics Committee approval was obtained (date: 21.03.2022, no: 76).

**Informed Consent:** Participants provided informed consent if they agreed to participate in the further studies.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: S.T., Z.Ö.G., T.Y.P., Concept: B.K.A., Ö.Ç., T.Y.P., İ.Ü., Design: B.K.A., S.T., İ.Ü., Data Collection or Processing: Z.Ö.G., T.Y.P., Analysis or Interpretation: B.K.A., Ö.Ç., İ.Ü., Literature Search: B.K.A., Z.Ö.G., Writing: B.K.A., Ö.Ç., S.T.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Effectiveness of the Fibrosis-4 Score in Predicting Intrahepatic Cholestasis of Pregnancy

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## Abstract

**Objective:** To investigate the role of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet values in predicting intrahepatic cholestasis of pregnancy (ICP) together with the fibrosis-4 (FIB-4) score.

**Methods:** This study consisted of a patient group diagnosed with ICP (n=44) and a control group (n=53). Laboratory tests of both groups were analyzed retrospectively. Receiver operating characteristic (ROC) analysis was performed to determine cut-offs for first trimester FIB-4 score, AST, ALT and platelet values to predict the development of ICP.

**Results:** The first trimester FIB-4 score, AST, ALT values were found to be statistically significantly higher, and the platelet value was found to be statistically significantly lower in the study group. The first trimester FIB-4 score was statistically significant in predicting the development of ICP in the third trimester (p value 0.001), and the ROC value was 0.741. When the cutoff value for the FIB-4 score is set as  $\geq 0.425$ , the sensitivity is 77.3% and the specificity is 54.7%.

**Conclusion:** First trimester FIB-4 score was found to be effective in predicting ICP. Additionally, the first trimester AST, ALT and platelet values were found to be effective in the prediction of ICP diagnosed at the third trimester.

**Keywords:** FIB-4 score, intrahepatic cholestasis, pregnancy

## Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a disease diagnosed in the late second or third trimester of pregnant women without any accompanying liver or biliary tract pathology with reported incidence rates of between 0.2% and 2% (1). It classically presents with pruritus that commonly includes the palms and soles, and biochemical evidence of abnormal liver function, and raised serum bile acid levels (1). The pathophysiology of intrahepatic cholestasis remains unclear, it is thought that many factors related to genetic predisposition, reproductive hormones, and environmental factors play key roles in pathogenesis of ICP (2). The risk of pregnancy complications, such as perinatal

death, antenatal passage of meconium, spontaneous preterm birth, intrapartum fetal distress and anoxia, increases in the short term (perinatal period) due to ICP (3,4). In the long term after ICP, it has been reported that the risk of hepatobiliary diseases, autoimmune diseases, cardiovascular diseases and cancer development increases (5). Determining the pregnant group at risk in terms of ICP at early gestational weeks may make it possible to take precautions, at least for short-term complications. However, it is seen that there are few studies on this purpose in the literature.

The fibrosis-4 (FIB-4) score, which is a non-invasive marker, is effective in predicting fibrosis in liver diseases (6,7). However,



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**Cite this article as:** Gök K, Takmaz T, Köse O, Tüten N, Bostancı MS, Özden S. Effectiveness of the Fibrosis-4 Score in Predicting Intrahepatic Cholestasis of Pregnancy. Eur Arch Med Res 2022;38(4):299-303

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European Archives of Medical Research published by Galenos Publishing House.

**Received:** 29.01.2022

**Accepted:** 26.04.2022

there is no study investigating the effectiveness of FIB-4 score in predicting ICP in early gestational weeks. In this first study, we investigated the role of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet levels in predicting ICP together with FIB-4 score.

## METHODS

In this study, we identified singleton deliveries occurring from the beginning of the year January 2017 until February 2021 who applied to Sakarya University Training and Research Hospital, Clinic of Obstetrics and Gynecology in the early period of pregnancy, followed up. The diagnosis of ICP was based on characteristic symptoms, as well as elevated serum fasting bile acid level ( $\geq 10 \mu\text{mol/L}$ ) in maternal bloods, in the absence of other hepatobiliary disease (8). Forty-four pregnant women diagnosed with ICP according to these criteria were identified. Fifty-three healthy pregnant women with similar age and body mass index (BMI) were determined as the control group. We excluded twins and higher multiples, pregnant women with chronic systemic diseases such as pregestational or gestational diabetes, liver and biliary tract disease, hematological disease, dermatological disease, infectious disease because they have a higher incidence of complications during pregnancy. Approval was obtained from the local ethics committee for the study. Patient information was obtained from medical records.

In both groups, age, gravida, parity, BMI, first and third trimester platelet, AST and ALT levels and maternal blood fasting bile acid levels at the time of diagnosis were recorded. The FIB-4 score was calculated using Sterling's formula [ $\text{age (years)} \times \text{AST (IU/L)} / \text{platelet count (109/L)} \times \sqrt{\text{ALT (IU/L)}}$ ] (9).

This study was designed in accordance with the Declaration of Helsinki Principles and was approved by the Sakarya University Faculty of Medicine Ethics Committee on January 29, 2021 (ethics no: E-71522473-050.01.04-578804).

### Statistical Analysis

Statistical analysis were performed using the SPSS 24.0 package program (SPSS Inc. and Lead Tech. Inc. Chicago. USA). Kolmogorov-Smirnov test was used in compliance with normal distribution. Comparison of the levels of variables with normal distribution between study and control groups was made by Student's t-test, and the comparison of variables with non-normal distribution was made the Mann-Whitney U test. Parametric variables are shown as mean  $\pm$  standard deviation and non-parametric variables with median (minimum-maximum). Spearman correlation test was performed to evaluate the possible relationship between

first trimester FIB-4 score and third trimester maternal fasting bile acid value. Receiver operating characteristic (ROC) analysis was performed to determine cut-off for first trimester FIB-4 score to predict the development of ICP. A value of  $p < 0.05$  was considered significant.

## RESULTS

Baseline characteristics of the study population are shown in Table 1. There was no statistically significant difference between the study and control groups in terms of age, BMI, gravida, and parity ( $p > 0.05$ ). There were statistically significant differences between the study and control groups in terms of the first trimester FIB-4 score ( $0.538 \pm 0.196$  vs.  $0.405 \pm 0.073$ ; respectively,  $p = 0.001$ ), AST level ( $22.26 \pm 11.44$  vs.  $16.15 \pm 3.44$ ; respectively,  $p = 0.001$ ) and ALT level ( $27.64 \pm 24.2$  vs.  $14.55 \pm 5.49$ ; respectively,  $p = 0.001$ ). The first trimester FIB-4 score, AST, ALT levels were found to be statistically significantly higher, and the first trimester platelet level was found to be statistically significantly lower in the study group compared to the control group, even if it was within the normal reference range ( $244.20 \pm 56.54$  vs.  $285.54 \pm 56.85$ ; respectively,  $p = 0.001$ ) (Table 1).

While the third trimester FIB-4 score ( $0.92 \pm 0.31$  vs.  $0.62 \pm 0.20$ ; respectively,  $p = 0.001$ ), AST ( $82.18 \pm 45.81$  vs.  $19.02 \pm 6.77$ ; respectively,  $p = 0.001$ ), ALT ( $118.55 \pm 76.47$  vs.  $12.06 \pm 4.55$ ; respectively,  $p = 0.001$ ) levels were found to be statistically significantly higher in the study group compared to the control group, there was no statistically significant difference in terms of platelet levels ( $241.50 \pm 58.91$  vs.  $247.56 \pm 58.41$ ; respectively,  $p = 0.614$ ) (Table 2).

When the results were evaluated, no correlation was found between the 1<sup>st</sup> trimester FIB-4 score and third trimester maternal blood fasting bile acid level ( $p = 0.785$ ).

When the development of ICP was evaluated, it was determined that the first trimester FIB-4 score, AST, ALT and platelet levels were predictive (Table 1). The first trimester FIB-4 score was statistically significant in predicting the development of ICP in the third trimester ( $p = 0.001$ ), and the ROC value was 0.741. When the cut-off value for the FIB-4 score is set as  $\geq 0.425$ , the sensitivity is 77.3% and the specificity is 54.7% (Figure 1).

## DISCUSSION

Although biopsy is the most specific test to assess the nature and severity of liver diseases and grading inflammation and fibrosis, it has disadvantages such as high cost, serious complication risk, significant sampling error and inter/intra observer variability



**Table 1. Baseline characteristics of patients in the first trimester of pregnancy**

Variables	Without cholestasis (n=53)		With cholestasis (n=44)		p value
	Mean $\pm$ SD	Median (min-max)	Mean $\pm$ SD	Median (min-max)	
Age (years)	27 $\pm$ 5	26 (17-40)	28 $\pm$ 4	28 (19-38)	0.240
Gravida	2.4 $\pm$ 1.1	2 (1-5)	2.25 $\pm$ 1.12	2 (1-5)	0.436
Parity	1.13 $\pm$ 0.86	1 (0-3)	0.91 $\pm$ 0.83	1 (0-3)	0.168
Body mass index	25.75 $\pm$ 1.07	25.8 (24-28.6)	25.97 $\pm$ 1.84	26.15 (21.2-29.3)	0.477
AST (IU/L)	16.15 $\pm$ 3.44	16 (11-25)	22.26 $\pm$ 11.44	18 (12-67)	<b>0.001</b>
ALT (IU/L)	14.55 $\pm$ 5.49	13 (7-31)	27.64 $\pm$ 24.2	18 (7-114)	<b>0.001</b>
Platelet (10 <sup>9</sup> /L)	285.54 $\pm$ 56.85	275 (193-443)	244.20 $\pm$ 56.54	233 (153-388)	<b>0.001</b>
FIB-4 score	0.405 $\pm$ 0.073	0.42 (0.19-0.52)	0.538 $\pm$ 0.196	0.5 (0.24-1.24)	<b>0.001</b>

Values are expressed as mean  $\pm$  SD, median (min-max). p<0.05, statistically significant difference. SD: Standard deviation, min: Minimum, max: Maximum, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FIB-4: Fibrosis-4

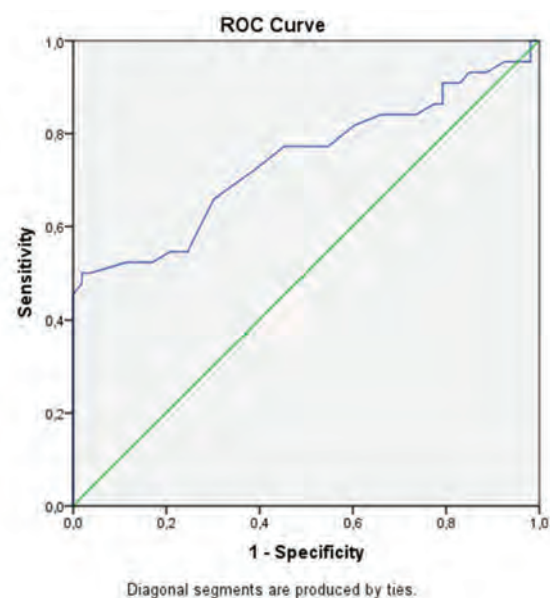
**Table 2. Baseline characteristics of patients in the third trimester of pregnancy**

Variables	Without cholestasis (n=53)		With cholestasis (n=44)		p value
	Mean $\pm$ SD	Median (min-max)	Mean $\pm$ SD	Median (min-max)	
AST (IU/L)	19.02 $\pm$ 6.77	9 (18-46)	82.18 $\pm$ 45.81	64.5 (27-210)	<b>0.001</b>
ALT (IU/L)	12.06 $\pm$ 4.55	11 (6-28)	118.55 $\pm$ 76.47	100 (15-331)	<b>0.001</b>
Platelet (10 <sup>9</sup> /L)	247.56 $\pm$ 58.41	245 (156-366)	241.50 $\pm$ 58.91	240 (144-443)	0.614
Total bilirubin (mg/dL)	-	-	0.94 $\pm$ 0.64	0.78 (0.20-3.20)	-
ALP (IU/L)	-	-	195.82 $\pm$ 68.45	182 (102-403)	-
GGT (IU/L)	-	-	26.61 $\pm$ 33.80	18 (6-225)	-
Fasting bile acid	-	-	29.52 $\pm$ 29.38	16.35 (10.2-129.3)	-
FIB-4 score	0.62 $\pm$ 0.20	0.58 (0.31-1.08)	0.92 $\pm$ 0.31	0.84 (0.31-1.74)	<b>0.001</b>

Values are expressed as mean  $\pm$  SD, median (min-max). p<0.05, statistically significant difference. SD: Standard deviation, min: Minimum, max: Maximum, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FIB-4: Fibrosis-4, ALP: Alkaline phosphatase GGT: Gamma-glutamyl transferase

(10-12). Therefore, some invasive methods have been developed to replace liver biopsy for prediction of the liver damage (13,14). Complete blood count, routine biochemistry parameters, AST to platelet ratio index (APRI), albumin-bilirubin score (ALBI) and FIB-4 score are used in the calculation of some of these methods (6,15-17). After the FIB-4 score was first described by Sterling et al. (9), its effectiveness in various liver diseases was investigated and it was stated that it could be a reliable marker in showing the progression of the disease (17,18).

In a study conducted on women with chronic liver disease in which the relationship between ALBI and APRI scores in the preconceptional period and pregnancy outcomes was evaluated, it was found that the ALBI score was effective in predicting live birth and the APRI score beyond 37 weeks of gestation (19). In this study, pre-pregnancy ALBI and APRI scores were valuable in predicting pregnancy outcomes in pregnant women with previously known liver disease (19), whereas in our study, the first trimester FIB-4 score in pregnant women without liver

**Figure 1.** ROC curve of first trimester FIB-4 score to the diagnosis of intrahepatic cholestasis in pregnancy

ROC: Receiver operating characteristic, FIB-4: Fibrosis-4



disease was found valuable in predicting a liver diseases seen during pregnancy, such as ICP. These results suggest that these markers can be used for different purposes in pregnant women with and without liver disease during pre-pregnancy and early pregnancy.

The value of various markers in the prediction of ICP development in early pregnancy was investigated and the decrease in first trimester PAPP-A MoM value and the high level of total cholesterol, low-density lipoprotein cholesterol and sulfated metabolites of progesterone were found to be valuable (20-22). Similar to these studies, evaluating the high FIB-4 score, which is found to be significant in predicting ICP in the early weeks of gestation, may help develop treatment strategies to prevent maternal and fetal complications that may develop due to this disease.

In another study designed similarly to our study, the efficiency of the first trimester APRI score in ICP estimation was evaluated, and the first trimester APRI score was found to be high in pregnant women with cholestasis, and, a positive correlation was found between APRI score and fasting bile acid levels (23). Although we found the first trimester FIB-4 score to be high in pregnant women who developed cholestasis, we could not find any correlation between the first trimester FIB-4 score and fasting bile acid levels. In our study, the first trimester FIB-4 score was found to be  $0.53 \pm 0.19$  in those with cholestasis and  $0.40 \pm 0.07$  in those who did not. These values are considerably lower than the FIB-4 score values in studies conducted with patients with known liver disease, indicating that patient selection was good (15,16,24). Tolunay et al. (23) found that the first trimester APRI score of  $0.7 \pm 0.1$  in pregnant women with cholestasis and  $0.4 \pm 0.2$  in pregnant women who did not. The fact that the APRI score in pregnant women with cholestasis is close to those with liver disease suggests that the patient selection in this study may not have been correct (15,16). This may be due to a liver disease affecting the biliary system, which could not be detected before the development of ICP in these patients. This may have led to a correlation between the APRI score and fasting bile acid, although we could not detect it with the FIB-4 score. Additionally, in our study, although AST level, ALT level and platelet level used in the calculation of FIB-4 score in the first trimester were found to be valuable in predicting ICP, although they were in the normal reference range, it was determined that FIB-4 score was the best prediction. Although the ICP prediction levels of the APRI score and the first trimester FIB-4 score were not compared in this study, the FIB-4 score may provide an advantage in prediction since it includes more parameters such as age and ALT level than the APRI score. Calculation of non-invasive markers with

these parameters, which are frequently used in routine clinical practice, can be an alternative to invasive methods in the evaluation of any pregnancy-related liver disease, including ICP.

The reason why these markers can be used to determine fibrosis in liver diseases is thrombocytopenia due to portal hypertension and elevation of AST and ALT levels due to liver damage. Even if the main use of FIB-4 score is to determine fibrosis in liver diseases, it is interesting that it predicts a situation where fibrosis is minimal or absent, such as ICP. This suggests that liver damage, which cannot be detected by evaluating a single parameter and does not progress with fibrosis, can be detected with these markers calculated using multiple parameters. In a study conducted on non-alcoholic fatty liver patients with no or mild fibrosis detected in liver biopsy, portal hypertension was detected around 12%, supporting this idea (25). Accordingly, although liver fibrosis cannot be demonstrated pathologically in patients with ICP, it can be noted that there are changes at the molecular level.

### Study Limitations

The limitations of this study include its retrospective nature, lack of perinatal results, and absence of biopsy to evaluate liver pathology in pregnant women with cholestasis.

## CONCLUSION

In conclusion, the first trimester FIB-4 score was found to be effective in predicting ICP in this first study. This score can help detect liver diseases in early pregnancy and thus preventing disease progression with appropriate treatment.

### Ethics

**Ethics Committee Approval:** This study was designed in accordance with the Declaration of Helsinki Principles and was approved by the Sakarya University Faculty of Medicine Ethics Committee on January 29, 2021 (ethics no: E-71522473-050.01.04-578804).

**Informed Consent:** The study had a retrospective design, because of that patient consent was not obtained.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: K.G., O.K., M.S.B., S.Ö., Design: K.G., O.K., N.T., M.S.B., S.Ö., Data Collection or Processing: K.G., O.K., M.S.B., Analysis or Interpretation: K.G., T.T., N.T., Literature Search: K.G., T.T., N.T., M.S.B., S.Ö., Writing: K.G., T.T., S.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Treatment of Abnormal Uterine Bleeding Due to a Leiomyoma in a Bicornuate Uterus with Uterine Artery Embolization: The First Case in the Literature

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## Abstract

Uterine leiomyomas constitute an important group of abnormal uterine bleeding (AUB) according to International Federation of Gynecology and Obstetrics classification system (PALM-coein). Bicornuate uterus anomaly is the 3<sup>rd</sup> most common uterine anomaly and the combination of these two entities is also rare. We present 46 years old gravida 1, para 1 women suffering from AUB for 6 years. There was bicornuate retroverted uterus image with 2 different endometrial cavities and 5 cm class 2 leiomyoma according to PALM-coein classification. Oral progesterone treatment was insufficient formerly and she refused hysterectomy or myomectomy procedures. Because she is not suitable for intrauterine levonorgestrel treatment, she was discussed with the interventional radiologists and planned for uterine artery embolization (UAE). Maximum diameter of 54 mm intramural myoma on magnetic resonance imaging before embolization was shrunk to 39 mm at the 6<sup>th</sup> month of intervention with no further anemia, AUB, and fatigue. This is the first case report representing the treatment of uterine leiomyoma in a bicornuate uterus with a successful UAE despite its uterine anomaly. UAE is a reliable technique in patients refusing surgery and predicted to have a risky and difficult operation, if performed by experienced interventional radiologists.

**Keywords:** Abnormal uterine bleeding, leiomyoma, bicornuate uterus, uterine artery embolization

## INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the most common reasons for gynecology outpatient clinic admission of women of reproductive age. It has a wide range and disturbs the quality of life leading to emotional, social, sexual, financial, and medical burdens (1). To standardize this wide range of bleeding pattern International Federation of Gynecology and Obstetrics (FIGO) classification system 2 (PALM-coein) was declared in 2011 and the classification was grouped as polyp(s), adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic, and not yet classified (2). Leiomyomas as

a member of AUB has also subgroups according to PALM-coein and there are many ways of managing these benign lesions including medical, surgical, or interventional (3).

Uterine anomalies are another issue and the most common type of female genital tract anomalies that has the approximate prevalence of 2-10% among women of reproductive age (4). Although it is not classified with PALM-coein, bicornuate uterus anomaly is the 3<sup>rd</sup> most common uterine anomaly coming after arcuate uterus and uterine septum in which the etiology is incomplete fusion of the müllerian duct with two communicating endometrial cavities (5).



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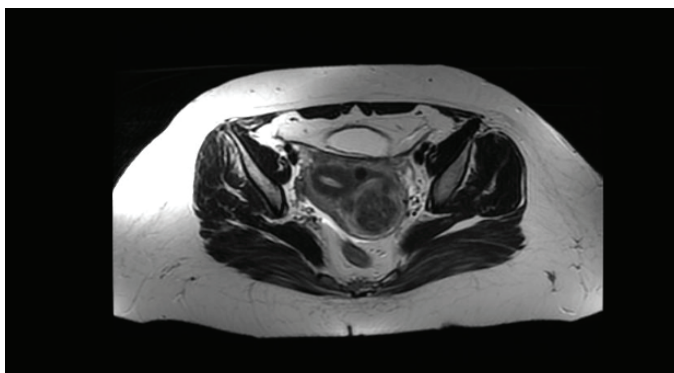
**Received:** 09.04.2022  
**Accepted:** 02.11.2022

**Cite this article as:** Ketenci Gencer F, Gürkan O, Hasanefendioğlu Bayrak A, Kobaner Cankoy N. Treatment of Abnormal Uterine Bleeding Due to a Leiomyoma in a Bicornuate Uterus with Uterine Artery Embolization: The First Case in the Literature. Eur Arch Med Res 2022;38(4):304-307

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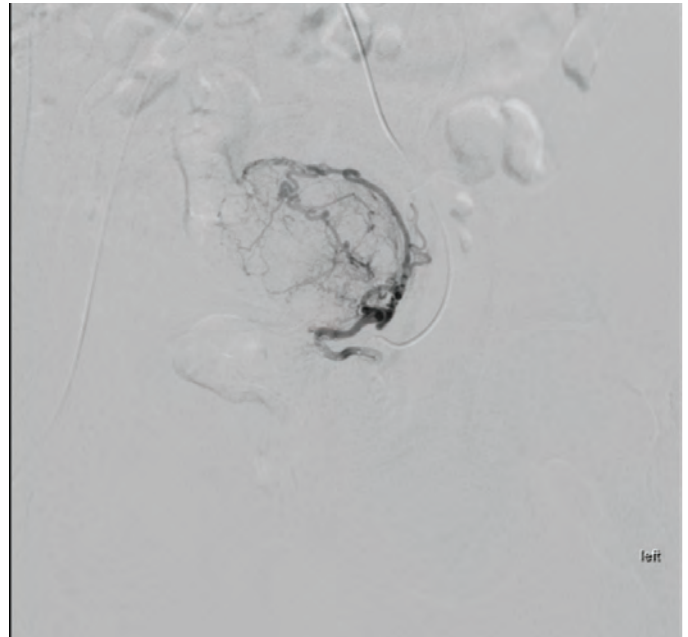
## CASE PRESENTATION

We present 46 years old gravida 1, para 1 women suffering from AUB for 6 years. She had been using diapers instead of classic sanitary pads due to heavy menstrual bleeding. However, especially in the first 2 or 3 days of menstruation, diapers were not sufficient. She stated that during her menstrual period, she feels dizziness, palpitation, fatigue, and cold. She was prescribed for anti-anemics for many times formerly and still using but she did not benefit. In her physical examination, she was pale with a body mass index of 40.7. She had grade 1 perineal laceration due to vaginal delivery and normal cervix on speculum. There was bicornuate retroverted uterus image with 2 different endometrial cavities and 5 cm type 2 leiomyoma according to PALM-coein classification on the left horn of the uterus and compressing the endometrial cavity under transvaginal ultrasound. Her hemoglobin level was 9.1 g/L, and hematocrit was 29%. The magnetic resonance imaging (MRI) revealed 55 cm<sup>3</sup> with a maximum diameter of 54 mm intramural myoma and additional leiomyomas with a diameter of less than 1.5 cm without any suspicion of malignancy (Figure 1). Three endometrial samplings performed formerly revealed no sign of malignancy. She had used oral progesterone, but no positive effect was observed on uterine bleeding and intrauterine levonorgestrel could not be scheduled due to her uterine anomaly. Myomectomy was not discussed due to her age and her body mass index was another morbidity. Nonetheless, total hysterectomy was offered but she avoided any type of organ losing operation. Then she was discussed with the interventional radiologists. After informing the patient in detail, she was planned for uterine artery embolization (UAE) despite her uterine anomaly. All possible scenarios during the operation were informed to the patient before the procedure. UAE was performed with a high concentration to be sure about the vessel anatomy. Five-F (french) introducer sheath was introduced through right common femoral artery after local anesthesia was applied. Five-F catheter was guided into the

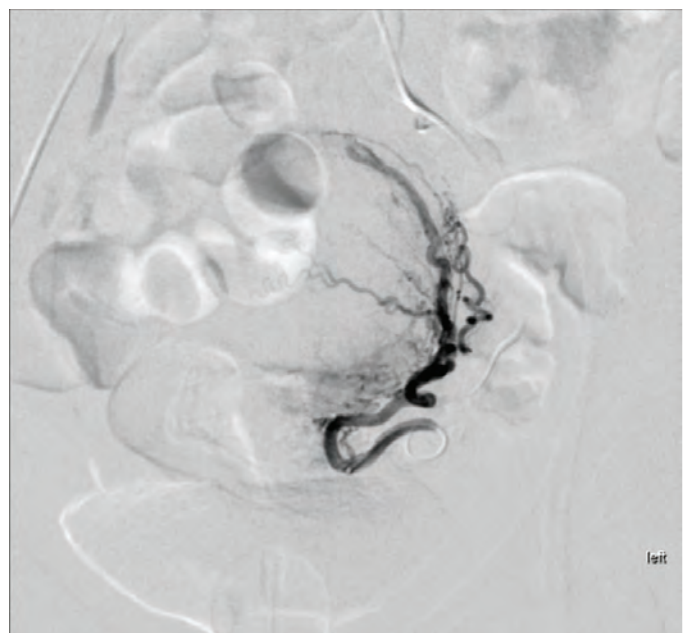


**Figure 1.** 54 mm type 2 leiomyoma shown in the magnetic resonance imaging before uterine artery embolization

internal iliac artery. After contrast injection, uterine artery was catheterized super selectively with microcatheter. Arteriography was performed with 5-10 mL on contrast on each uterine artery (Figure 2). Microcatheter was placed after vaginal artery and embolizing drug was injected until achieving the stasis of contrast material. 350-500  $\mu$ m and 500-700  $\mu$ m polyvinyl alcohol particles were used for embolization. Contrast injection image of post-embolization was also determined (Figure 3). After



**Figure 2.** Axial T2 weighted contrast-enhanced magnetic resonance imaging before uterine artery embolization

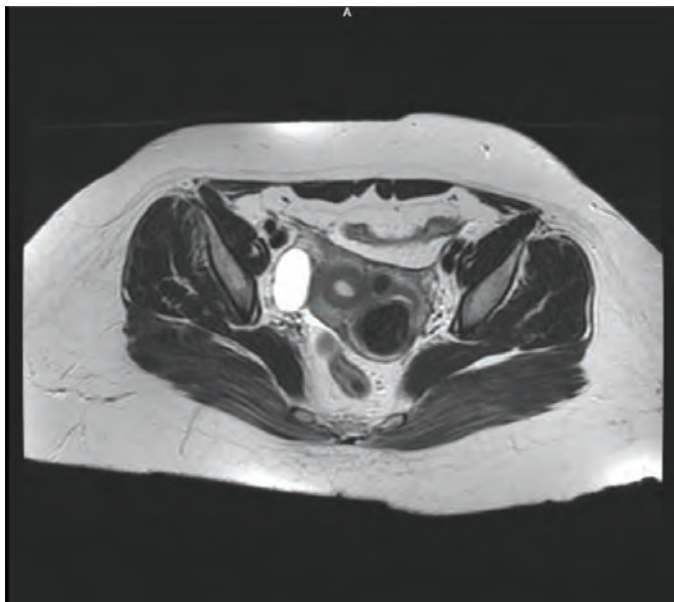


**Figure 3.** Axial T2 weighted contrast-enhanced magnetic resonance imaging after uterine artery embolization



both embolization of uterine arteries was made, catheters were removed and pressure bandage over the wound was placed. During and after the procedure no complication was observed.

The first control visit was performed 1 month after the embolization and the clinical symptoms decreased in severity with less bloody menstrual period but still using diapers. On her second visit at the 6<sup>th</sup> month, the size of the leiomyoma was shrunk to 39 mm on MRI with normal menstrual bleeding (Figure 4). Her last hemoglobin and hematocrit level was 11 g/L and 35%, respectively. Fatigue disappeared and no additional signs were felt during menstruation.



**Figure 4.** Shrunk leiomyoma with a diameter of 39 mm in the magnetic resonance imaging after 6 months of uterine artery embolization

## DISCUSSION

There are lots of clinical trials concerning embolization in leiomyoma especially for patients refusing surgery. Ravina et al. (6) was a researcher firstly applied UAE to their patients and achieved a significant success rate. Dutton et al. (7) compared the effectiveness of UAE and hysterectomy and revealed that UAE has fewer complication rates but one-fourth of the UAE patients needed additional treatment modality for their leiomyomas in their multicenter retrospective study. They also concluded that both modalities are safe and effective for treatment of leiomyomas (7). Manyonda et al. (8) compared myomectomy procedure with UAE and showed that menstrual bleeding scores were similar after interventions. The rate of additional treatment for harboring bleeding was 7% for myomectomy and 16% for UAE (8). On the light of these information, our case was also a candidate for UAE but the confounding factor was the presence

of bicornuate uterus anomaly. A successful embolization was performed by talking to the patient in detail, and we observed that the patient's complaints resolved and did not recur during the follow-up period.

## CONCLUSION

To conclude, this is the first case in the literature of a symptomatic leiomyoma in a bicornuate uterus treated with UAE. Although the anatomy of the vessels was a bit difficult in accordance with the anatomy of bicornuate uterus, it was not so complicated and there was no need to end up the procedure. This case may also be a good example for managing symptomatic leiomyomas in not only in bicornuate uterus but also other types of uterine anomaly in patients refusing surgery. UAE can be a reliable technique if performed by experienced interventional radiologists.

## Ethics

**Informed Consent:** Patient consent for publication was obtained for this case report.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: F.K.G., O.G., Concept: F.K.G., O.G., Design: F.K.G., Data Collection or Processing: F.K.G., O.G., N.K.C., A.H.B., Literature Search: F.K.G., O.G., N.K.C., Writing: F.K.G., O.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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# Ruptured Collateral Venous Aneurysm Associated with IVC Agenesis Resulting in a Massive Retroperitoneal Hematoma

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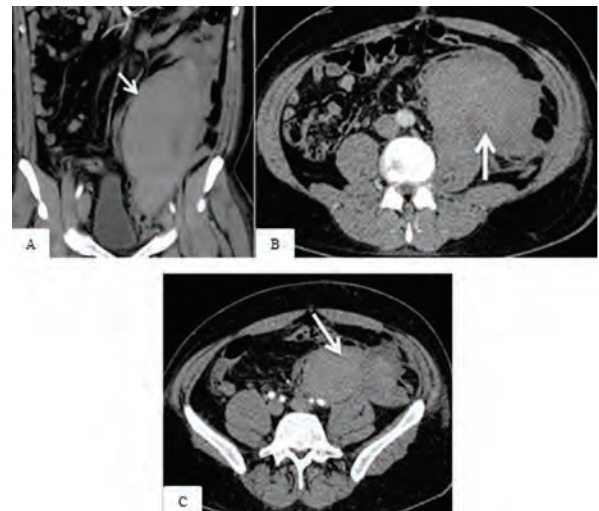
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**Keywords:** IVC agenesis, retroperitoneal hematoma, deep vein thrombosis

Dear Editor,

The embryonic development of inferior vena cava (IVC) is a complex process with regressions and anastomoses of embryonic veins. Congenital abnormalities of the IVC and its tributaries were first described by Abernethy (1) in 1793 with the demonstration of a congenital mesocaval shunt and continuation of IVC with azygos vein in a 10-month-old child. IVC agenesis (IVCA) is one of the rare anomalous developments of IVC having a controversial pathophysiological mechanism in which defective development of the embryonic veins and intrauterine/perinatal IVC thrombosis are both suggested (2). Many patients remain clinically silent but, it may also be diagnosed following its serious complications, most commonly unprovoked multiple deep vein thromboses (DVT) in young individuals, particularly in the lower extremities (3). However, unusual presentations may also occur. We present an extremely rare presentation of IVCA complicated by massive retroperitoneal hematoma (RPH) in a young patient with acute abdominal pain. A 35-year-old previously healthy young male person was admitted to the emergency department with acute onset left abdominal pain. He was hypotensive, and the laboratory findings showed decreased hemoglobin levels in addition to metabolic acidosis. He had no bleeding disorders and was not taking any anticoagulant treatment. IV contrast-enhanced abdominal computed tomography revealed a massive RPH with the largest diameter of 20 cm with a mass effect on adjacent structures. The arterial phase images

excluded the arterial etiology of the retroperitoneal bleeding (Figure 1). The intrahepatic IVC was absent with hypoplastic hepatic IVC. Superiorly, the hepatic veins were draining into the suprahepatic IVC. Inferiorly, the common iliac veins were draining into the dilated ascending lumbar veins, which in turn drain into the azygos/hemiazygos system via paravertebral varicoid collaterals, of which most were thrombosed (Figure 2). The renal veins were also draining into the dilated azygos system. A filling defect was observed in the joining part of the



**Figure 1.** (A-C) Arterial phase IV contrast-enhanced abdominal CT scan showing a massive RPH near the left side of the aorta with mass effect on the left bowel segments and the bladder (arrows)

IV: Inferior vena, CT: Computed tomography, RPH: Retroperitoneal hematoma



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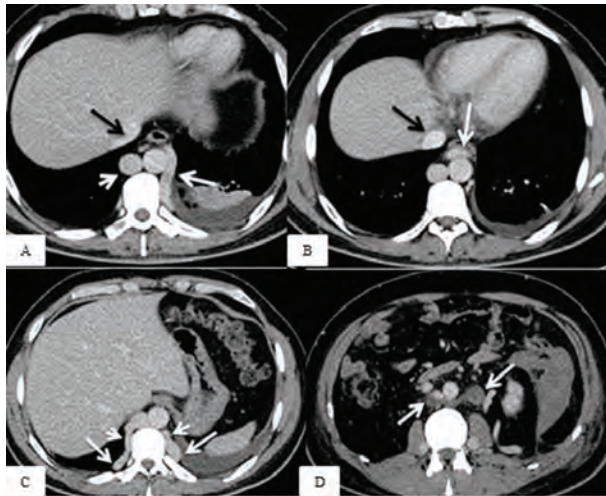
**Cite this article as:** Erok B, Win NN, Önder H. Ruptured Collateral Venous Aneurysm Associated with IVC Agenesis Resulting in a Massive Retroperitoneal Hematoma. Eur Arch Med Res 2022;38(4):308-309

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**Received:** 30.09.2021

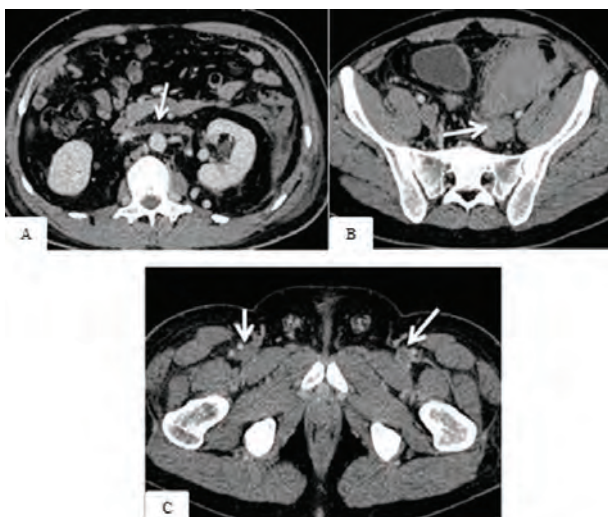
**Accepted:** 02.07.2022

renal veins but attributed to an admixture artifact rather than a thrombus due to the lack of renal parenchymal findings of venous congestion. There was a tubular retroperitoneal aneurysmal lumbar collateral vein, very close to the hematoma, whose rupture was probably caused the large hematoma. DVT of bilateral external iliac veins was also noted (Figure 3). In addition



**Figure 2.** (A-D) The hypoplastic hepatic IVC (A, black arrow) and the normal suprahepatic IVC (B, black arrow) are shown. Note the dilated azygous vein (A, B, short white arrow), dilated accessory hemiazygous vein (A, B, white arrow), and dilated ascending lumbar veins (C, white arrows) which in turn drain into the azygous and hemiazygous system via paravertebral varicoid collateral (C, short white arrows) veins. Thrombosed collateral veins are shown (D, arrows)

IVC: Inferior vena cava



**Figure 3.** The renal veins draining into the dilated azygous system are shown. The filling defect in the joining part of the renal veins that was attributed to an admixture artifact is visible (A, arrow). A large tubular retroperitoneal structure among the dilated paravertebral collateral vessels interpreted as a likely aneurysmal left lumbar collateral vein whose rupture had caused the large hematoma is shown (B, arrow). DVT of bilateral EIVs was also noted (C, arrows)

DVT: Deep vein thromboses, EIVs: External iliac veins

to the continuation of the fluid and erythrocyte replacement, low-molecular-weight heparin was added to the treatment and he was referred to the cardiology department for follow-up. Hemoglobin levels started to increase with the correction of the metabolic acidosis and blood pressure. With the concern of malignant involvement of the veins, especially from testis tumors, scrotal Doppler ultrasonography was performed and did not reveal any pathology. The final diagnosis was spontaneous rupture of the aneurysmal compensatory collateral paraspinal veins resulting in a massive RPH. In conclusion, spontaneous RPH is a very rare clinical entity that typically occurs in patients who are receiving anticoagulation or hemodialysis. It is an extremely rare complication of IVCA. Although the collateral paraspinal veins are important ways for sustaining venous return in these patients, they can become so dilated that they are aneurysmal and ruptured, as in this study.

### Ethics

**Informed Consent:** Verbal informed consent has been taken from the patient.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: B.E., H.Ö., Design: B.E., N.N.W., H.Ö., Data Collection or Processing: B.E., Analysis or Interpretation: B.E., N.N.W., H.Ö., Literature Search: B.E., N.N.W., Writing: B.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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