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## Original Articles



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| Review Article | 5000 | 250 | 50 | 6 | 10 or total of 20 images |
| Case Report | 1000 | 200 | 15 | No tables | 10 or total of 20 images |
| Letter to the Editor | 500 | No abstract | 5 | No tables | No media |

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### Case Reports

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# The Analysis of the Frequency of Schmorl's Nodes on the Base of Modic Degeneration as Seen on the Lumbar Magnetic Resonance Imagings of the Cases with Lumbar Pain

## Bel Ağrılı Olguların Lomber Manyetik Rezonans Görüntülemelerinde Modik Dejenerasyon Zemininde Schmorl Nodülü Sıklığının İncelenmesi

Aysel Gürcan Atçı[1], İbrahim Burak Atçı[2]

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## ABSTRACT

**Introduction:** The aetiology of lumbar pain is multifactorial. One of the primary factors among these is disc degeneration, and degenerative processes lead to endplate changes. This study aimed to determine the incidence rate of Schmorl's nodes (SN), especially those accompanied by modic changes, among cases with lumbar magnetic resonance imaging (MRIs) performed as part of their clinical examination upon arrival at the clinic due to lumbar pain.

**Methods:** This study consisted of 128 patients who were admitted with low back pain and lumbar MRI were taken into the process. Age, gender, pain level has been recorded. All lumbar spinal disc spaces It has been evaluated. The incidence and sizes of the SN reveal SN observed especially with modic degeneration It has been studied in detail.

**Results:** The cases with and without modic degeneration were evaluated using the significance test for the difference between two proportions, and the results were not statistically significant ($p>0.05$). The cases with modic type-1 and type-2 degenerations were evaluated separately, but the frequency was not statistically significant ($p>0.05$). The separate comparisons of type-1 and type-2 modic degenerations against type-3 resulted in a statistically significant difference ($p<0.05$).

**Conclusion:** This study aimed to analyse the prevalence of SN in cases that underwent lumbar MRI due to lumbar pain and to reveal the difference between the frequency, size and pain character of SN in levels with modic degeneration. This study suggests that especially oedematous cases bigger than 10 mm are triggered by type-1 and type-2 degenerations. Analgesic anti-inflammatory treatments can be applied as well as protective treatments and rehabilitative programmes in order to treat these cases. In case of chronic pain, it can be controlled with vertebral fusion, vertebroplasty cement application, bone strengthening and intradiscal operations.

**Keywords:** Modic degeneration, Schmorl nodule, back pain

## ÖZ

**Amaç:** Bel ağrısı pek çok etiyolojik faktöre bağlı olarak görülebilir. Bu faktörlerden öncelikle görülenlerden bir taneside disk dejenerasyonudur. Dejeneratif süreç end plate değişikliklere neden olur. Dejenere endplate Schmorl nodülü (SN) oluşumunu hızlandırabilir. Bu çalışmamızda bel ağrısı ile polikliniğe başvuran ve lomber manyetik rezonans görüntüleme (MRG) çekilen olgularda SN görülme oranı ve özellikle modik değişiklikle birlikte SN insidansı saptanmaya çalışılmıştır.

**Yöntemler:** Son 6 ay içinde bel ağrısı ağrısı ile başvuran ve lomber MRG çekilen 128 hasta işleme alınmıştır. Olgular yaş, cinsiyet, ağrı düzeyi kayıt altına alınmıştır. Tüm lomber spinal disk aralıkları değerlendirilmiştir. SN görülme sıklığı ve boyutları ortaya konulmuş özellikle modik dejenerasyon ile birlikte gözlenen SN ayrıntılı incelenmiştir.

**Bulgular:** Modik dejenerasyonlu olan olgularda SN görülme sıklığı, modik dejenerasyon olmadan SN görülme sıklığı arasındaki ilişki istatistiki olarak anlamlı bulunmamıştır ($p>0,05$). Modik dejenerasyonlu olgularda ise tip-1 dejenerasyon zemininde SN görülme sıklığı tip-2 dejenerasyon zemininde SN görülme sıklığı ile karşılaştırıldığında istatistiksel olarak anlamlı bulunmamıştır ($p>0,05$). Hem tip-1 dejenerasyon hem tip-2 dejenerasyonuna eşlik eden modik dejenerasyon sıklığı ayrı ayrı tip-3 dejenerasyona eşlik eden modik dejenerasyon sıklığı ile karşılaştırıldığında fark istatistiki olarak anlamlı bulunmuştur ($p<0,05$).

**Sonuç:** Çalışmamızda özellikle bel ağrılı lomber MRG çekilen olgularda SN sıklığını irdelemek ve özellikle de modik dejenerasyon olan seviyelerde SN sıklığı boyutu ve ağrı karakter farklılığını ortaya koymak amaçlanmıştır.Bizim serimizde özellikle çevresinde ödem olan ve çapı 10 mm daha büyük olguların modik tip-1 ve tip-2 dejenerasyon zemininde olduğunu ortaya koymuştur. Bu olguların tedavilerinde analjezik anti-enflamatuvar tedaviler yanında tutucu tedaviler rehabilitasyon programları yapılabilmekte olup kronik ağrılarda omurga füzyon cerrahisi, vertebroplasti sement uygulaması ile kemik güçlendirme ve intradiskal girişimlerle ağrı kontrolü sağlanabilir.

**Anahtar Kelimeler:** Modik dejenerasyon, Schmorl nodülü, bel ağrısı

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## Introduction

Lumbar pain is observed frequently among societies. Approximately 84% of all individuals experience a lumbar pain attack in a period of their lives (1). On the other hand, at least 40% of individuals were found to incur lumbar pain for 6 months (2). Lumbar pain also has socio-economic origins. According to a study carried out in the United States, lumbar pain is one of the major reasons for job loss and is responsible for 12.5% of all losses in labour (3).

The aetiology of lumbar pain is multifactorial. One of the primary factors among these is disc degeneration. Disc degeneration is a progressive process that may arise due to various reasons, and degenerative processes lead to endplate changes. Bone marrow and endplate changes widely observed in spine magnetic resonance imagings (MRIs) were defined by modic. Modic changes are encountered as part of neuroradiologic processes during clinical practices.

On the other hand, Schmorl's nodes (SN) are frequently found in lumbar MRIs. SN were first defined by Christian Georg Schmorl, a German scientist (4). They are expressed as a nucleus pulposus not herniated into the vertebral canal, but into bone. In this respect, vertical disc protrusions are referred to as 'SN' (Figure 1).

This study aimed to determine the incidence rate of SN, especially those accompanied by modic changes, in the cases with lumbar MRIs performed as part of their clinical examination upon their arrival at the clinic due to lumbar pain.

## Methods

This study consisted of 128 patients who were consulted at the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinic of Neurosurgery within the last 6 months and were diagnosed with lumbar pain. The patients were required have performed lumbar MRIs following their anamnesis and examination results. All the MRIs were conducted with 1.5-T MRI (Siemens Magnetom Symphony, Erlangen, Germany). As a standard practice, T1-weighted spin-echo sequences [510/60/90/2 (TR/TE)] and axial and sagittal T2-weighted turbo spin-echo sequences (3480/102) were obtained. All the MRIs were interpreted by a radiologist.

All the intervertebral disc levels of the patients were assessed separately. The ages, genders and intervertebral disc levels of complaint of the cases were recorded.

The rates and dimensions of the SN and particularly, the SN with modic degeneration were recorded. Cases with trauma, malignancy, osteoporosis and disc operation history were excluded from the study. The patient's consent was not taken because it was a radiological archive study.

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision number: 2286, date: 10.05.2020).

### Statistical Analysis

Data were analysed using the IBM SPSS for Windows version 23.0 software (IBM Corp. Armonk, NY, USA). Frequency, percentage, mean, standard deviation, minimum and maximum were used for descriptive statistics. The results of the groups were analysed with Mann-Whitney U test. A value of $p<0.05$ was considered statistically significant.

## Results

The participants of this study were selected among the cases who were seen at the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinic of Neurosurgery between 01.10.2019 and 29.04.2020 due to lumbar pain. After the clinical examination, the patients were asked to do lumbar MRIs. Finally, the patients with SN and particularly, those with concomitant modic degeneration were included in this study. We entered keywords into the radiology archive to retrieve lumbar MRIs and performed the analyses on the images. A total of 128 cases with SN and 768 discs levels were examined, with the inclusion of the thoracolumbar junction. The population consisted of 74 female and 54 male patients. The mean age was 44.11+/-4.7 with the youngest and oldest patients being 21 and 79, respectively.

Among these, 78 cases (60.9%) showed millimetric SN in multiple levels, and their sizes varied between 0 and 10 mm. Modic type-1, modic type-2 and modic type-3 SN were found in 20 (15.6%), 29 (22.6%) and 1 (0.78%) patients, respectively (Figures 2-4). Regarding the cases with modic degeneration, 7 patients showed 10-20 mm and oedematous SN on modic type-1 degeneration base, while 5 cases showed 10-20 mm and oedematous SN on modic type-2 base. SN with modic degeneration was observed mostly at L4-5 levels, which corresponded to 21 cases. The second most frequent SN with modic degeneration was at the L5-S1 levels in 11 cases. Similarly, 4 cases with modic degeneration showed SN with the involvement of the L3-4 and L4-5 levels. On the other hand,

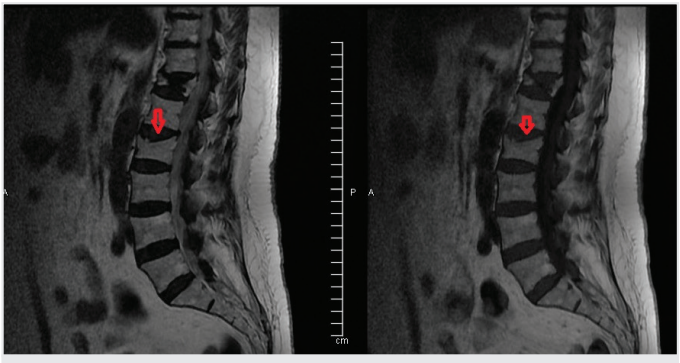

**Figure 1.** Schmorl nodule

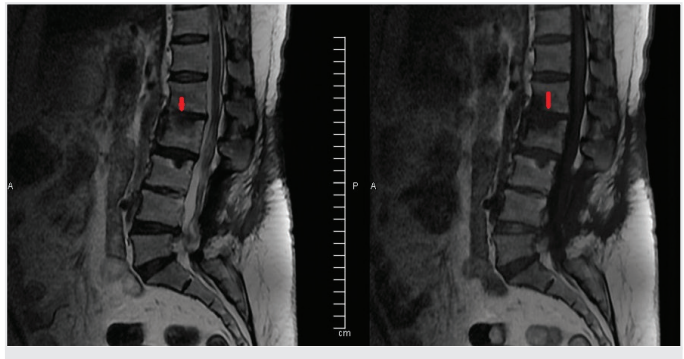

**Figure 2.** L1-2 Modic type-1 degeneration with Schmorl nodule

the cases who did not present modic degeneration had SN mostly at the L2-3 and L1-2 levels, respectively.

The cases of SN with and without modic degeneration were evaluated with the significance test for the difference between two proportions, and the results were not statistically significant ($p>0.05$). The cases of SN with modic type-1 and type-2 degenerations were evaluated separately, but the frequency did not show statistical significance ($p>0.05$). The separate comparisons of type-1 and type-2 modic degenerations with SN against type-3 modic degeneration with SN resulted in a statistically significant difference ($p<0.05$).

## Discussion

Lumbar pain is generally considered as a degenerative disc disease in aetiology. Neuroradiologically, lumbar pain shows a signal intensity with low degenerative disc material in T2-weighted imaging. McGregor was the first person to define degenerative lumbar disc in the aetiology of patients who came to consult due to chronic lumbar pain (5). Endplate changes are frequently observed during the progressive degeneration processes. De Roos et al. (6) defined endplate changes in the lumbar area for the first time in 1987, upon which Modic et al. (7) categorised these endplate changes under three groups. According to the MRIs, T1-weighted images demonstrated hypo-intensity in type-1 changes while T2-weighted images showed hyperintensity with fibrovascular tissue in the histopathological section; T1- and T2-weighted images suggested hyperintensity in type-2 changes with fat in the histopathological section; and T1- and T2-weighted images revealed hypo-intensity in type-3 changes with sclerotic bone in the histopathological section.

The cases with modic type-1 changes were generally defined as acute instability, acute degenerative disease, segmental instability and disc hernia. The incidence of lumbar pain is observed more in modic type-1 changes. On the other hand, fatty degeneration is present in modic type-2 changes, while a great part of these result from the progressive type-1 cases. Some studies propound that the percentage of symptomatic cases of type-2 is equal to type-1 (8). Type-3 endplate changes are associated with sclerosis. A part of the studies carried out on voluntary patients reported that degenerative endplate changes increased to 10 to 25% of their population (9).

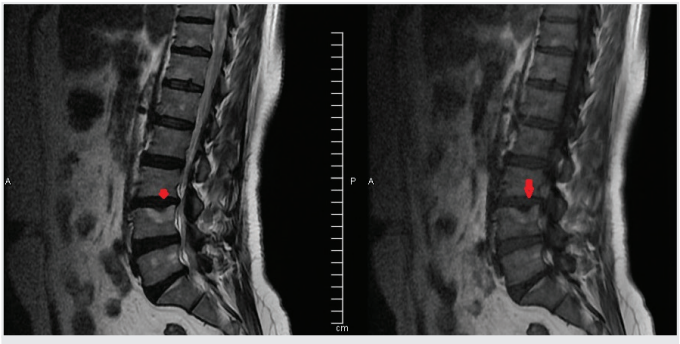

**Figure 3.** L4-5 Modic type-2 degeneration with Schmorl nodule

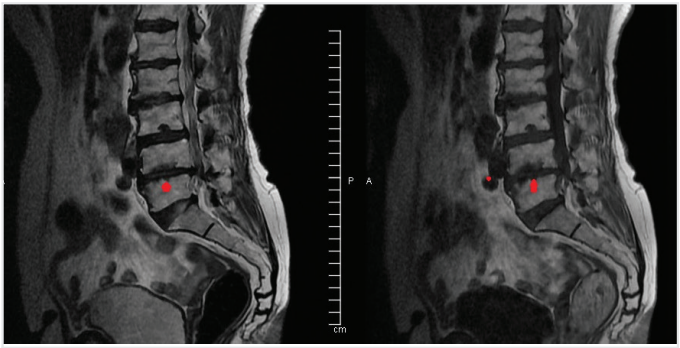

**Figure 4.** L4-5 Modic type-3 degeneration with Schmorl nodule

In 1927, Christian Georg Schmorl, a pathologist, defined a specific lesion in the corpus vertebrae and coined the term SN (10). SN are defined as nucleus pulposus not herniated into the central canal or foramen, but vertically into the bone through the cartilaginous tissue and endplate. They were found to be frequently associated with lumbar pain and following lumbar disc hernia (11). Although trauma, acute or chronic long-term exposition to axial loads, autoimmunity, advanced age, disc degeneration and degenerative bone diseases are alleged to be among the reasons that lead to SN, there is no consensus in the literature regarding its formation (12,13). Its prevalence varies between 38% and 79% in cadaver studies (14). In this study, the prevalence of multilevel SN was 51%. SN below 1 mm were observed frequently, especially in young adults. In another study, based on the MRIs of 150 maternal and 366 fraternal twins, it was asserted that they may have hereditary origins (15). Cases can show severe pain, but may also be asymptomatic. In this study, most of the cases followed the latter. However, the pain scores increased considerably especially in the SN cases accompanied by modic type-1 and type-2 degenerations.

This study aimed to analyse the prevalence of SN in cases with a lumbar MRI due to lumbar pain and to reveal the difference among the frequency, size and pain character of SN at levels with modic degeneration. The literature suggested that previous studies dwelt on the frequency of SN with lumbar disc degeneration. Disc degeneration increases in frequency with age and is observed in 50% and 80% of the population after 40 and 60, respectively (16,17). Williams et al. (15) reported that there is a correlation between SN and axial lumbar pain due to disc degeneration. It is also indicated that degenerative disc disease causes rupture in the annulus fibrosis and trigger nucleus pulposus herniation, while endplates decrease axial load resistance due to consequent degeneration. There is no study in the literature to draw attention to the relationship between modic changes and SN. This study suggests that especially oedematous cases bigger than 10 mm are triggered by type-1 and type-2 degenerations (Figure 5), and they show

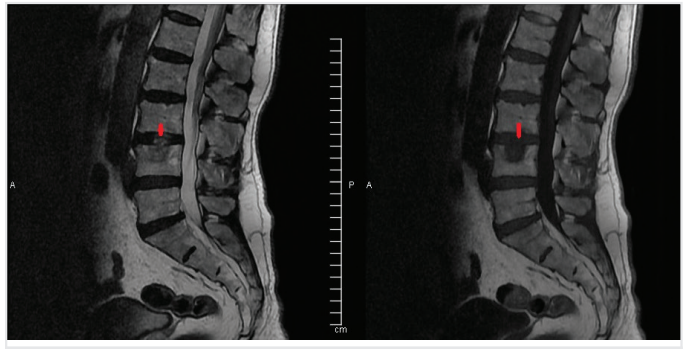

**Figure 5.** Oedematous case bigger than the 10 mm Schmorl nodule

severe pain. Analgesic and anti-inflammatory treatments can be applied as well as protective treatments and rehabilitative programmes in order to treat these cases. In case of chronic pain, it can be controlled with vertebral fusion, vertebroplasty cement application, bone strengthening and intradiscal operations.

## Conclusion

Lumbar pain is frequently observed in clinical practices with lumbar MRIs, as required in many cases. The source of pain can be diagnosed more easily and positive results can be achieved with correct treatment, if T1 and T2 sequence MRIs are carefully examined in middle age or elder cases with lumbar pain, modic changes are thus discovered and particularly, we diagnose SN concomitant with acute oedema as triggered by modic degeneration.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision number: 2286, date: 10.05.2020).

**Informed Consent:** The patient's consent was not taken because it was a radiological archive study.

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

**Authorship Contributions:** Surgical and Medical Practices - A.G.A., İ.B.A.; Concept - A.G.A., İ.B.A.; Design - A.G.A., İ.B.A.; Data Collection or Processing - A.G.A., İ.B.A.; Analysis or Interpretation - A.G.A., İ.B.A.; Literature Search - A.G.A., İ.B.A.; Writing - A.G.A., İ.B.A.

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

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## References

1. Walker BF. The prevalence of low back: a systematic review of the literature from 1966 to 1998. J Spinal Disord 2000; 13: 205-17.
2. Von Korff M, Dvorkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. Pain 1988; 32: 173-83.
3. Pittler MH, Karagülle MZ, Karagülle ME, Ernst E. Spa therapy and balneotherapy for treating low back pain. Rheumatology (Oxford) 2006; 45: 880-4.
4. Schmorl G, Junghanns H. The Human Spine in Health and Disease. Besemann EF, translator. 2th ed. New York: Grune and Stratton; 1971.
5. Keyes DC, Compere EL. The normal and pathological physiology of the nucleus pulposus of the intervertebral disc: an anatomical, clinical, and experimental study. J Bone Joint Surg Am 1932; 14: 897-938.
6. de Roos A, Kressel H, Spritzer C, Dalinka M. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. AJR Am J Roentgenol 1987; 149: 531-4.
7. Modic MT, Masaryk TJ, Ross JS, Carter JR. Imaging of degenerative disk disease. Radiology 1988; 168: 177-86.
8. Rahme R, Moussa R. The modic vertebral end plate and marrow changes: Pathologic significance and relation to low back pain and segmental instability of the lumbar spine. AJNR Am J Neuroradiol 2008; 29: 838-42.
9. Chung CB, Vande Berg BC, Tavernier T, Cotton A, Laredo JD, Vallee C, et al. End plate marrow changes in the asymptomatic lumbosacral spine: Frequency, distribution and correlation with age and degenerative changes. Skeletal Radiol 2004; 33: 399-404.
10. Schmorl G. Uber die an den wirbelbandscheiben vorkommenden ausdehnungs-und zerreisungsvorgange und die dadurch an ihnen und der wirbelspongiosa hervorgerufenen veranderungen. Verh Dtsch Path Ges 1927; 22: 250.
11. Coventry MB, Ghormley RK, Kernohan JW. The intervertebral disc: its microscopic anatomy and pathology. Part I. Anatomy, development, and physiology. J Bone Joint Surg Am 1945; 27: 105-12.
12. McGregor AH, Dore CJ, McCharty ID, Hughes SP. Are subjective clinical findings and objective clinical tests related to the motion characteristics of low back pain subjects? J Orthop Sports Phys Ther 1998; 28: 370-7.
13. Fahey V, Opeskin K, Silberstein M, Anderson R, Briggs C. The pathogenesis of Schmorl's nodes in relation to acute trauma. An autopsy study. Spine 1988; 23: 2272-5.
14. Hilton RC, Ball J, Benn RT. Vertebral end-plate lesions (Schmorl's nodes) in the dorsolumbar spine. Ann Rheum Dis 1976; 35: 127-32.
15. Williams FM, Manek NJ, Sambrook PN, Spector TD, Macgregor AJ. Schmorl's nodes: common, highly heritable, and related to lumbar disc disease. Arthritis Rheum 2007; 57: 855-60.
16. Lehto IJ, Tertti MO, Komu ME, Paajanen HE, Tuominen J, Kormano MJ. Age-related MRI changes at 0.1 T in cervical discs in asymptomatic subjects. Neuroradiology 1994; 36: 49-53.
17. Matsumoto M, Fujimura Y, Suzuki N, Nishi Y, Nakamura M, Yabe Y, et al. MRI of cervical intervertebral discs in asymptomatic subjects. J Bone Joint Surg Br 1998; 80: 19-24.

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# Malignant Mesothelioma in Cappadocia: Data from Eight Regional Hospitals

## Kapadokya Bölgesindeki Mezotelyoma: Sekiz Bölgesel Hastane Verileri

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## ABSTRACT

**Introduction:** This study aimed to describe the current situation of malignant mesothelioma (MM) by examining data from 8 state hospitals in Cappadocia, where one of the most serious mesothelioma endemics is observed. Recently, no assessment of this endemic has been conducted in Cappadocia. Therefore, this study aimed to provide up-to-date information regarding the current situation.

**Methods:** Patients with pleural or peritoneal MM admitted to local state hospitals in Cappadoccia between 01.01.2007 and 25.09.2019 were retrospectively evaluated. The primary endpoint of the study was the overall survival (OS). The secondary endpoint was the evaluation of the current status of MM cases in Cappadocia and the determination of patients' access to health care.

**Results:** Seventy-one patients were retrospectively evaluated. The median follow-up period was 26 months (range: 1-153); 55 patients (77.5%) died, while 16 patients (22.5%) survived. Sixty-six (93%) patients were diagnosed with pleural MM and 5 (7%) patients were diagnosed with peritoneal MM. It was observed that 18 (25.4%) of the patients resided in Sarıhıdır, Karain and Tuzköy, which was the decision to evacuate. Median OS was 16 months (range: 1-133) for pleural MM and 21 months (range: 9-117) for peritoneal MM. Significantly higher OS was observed in patients aged 60 years or less at the time of diagnosis (p=0.014). Only 6 patients (8.5%) were diagnosed at Nevşehir Hospital and 91.5% of 65 patients were diagnosed outside the Cappadoccia.

**Conclusion:** The current situation of MM in Cappadocia was evaluated in this study. The OS of MM patients has not changed dramatically in the last 30 years. Approximately 90% of patients had to move out of the province for diagnosis and treatment. Further studies are needed to evaluate the current situation and treatment outcomes in this region.

**Keywords:** Cappadocia, malignant pleural mesothelioma, malignant peritoneal mesothelioma

## ÖZ

**Amaç:** Bu çalışmanın amacı dünyanın en büyük mezotelyoma endemilerinden birine sahip olan Kapadokya'daki 8 devlet hastanesinin verilerini inceleyerek malign mezotelyomanın (MM) mevcut durumu hakkında bilgi vermektir. Son dekattır Kapadokya bölgesindeki endemi hakkında değerlendirme yapılmamış olup, çalışmamızda güncel durum hakkında bilgi vermek amaçlanmıştır.

**Yöntemler:** Kapadokya'daki yerel devlet hastanelerine 01.01.2007 ile 25.09.2019 tarihleri arasında başvuran plevral MM veya peritoneal MM hastaları retrospektif olarak değerlendirildi. Çalışmanın birincil sonlanım noktası genel sağkalım (OS) idi. İkincil sonlanım noktası, Kapadokya'daki MM olgularının mevcut durumunun değerlendirilmesi ve hastaların sağlık hizmetlerine erişiminin belirlenmesi idi.

**Bulgular:** Çalışmamızda 71 hasta retrospektif olarak değerlendirildi. Medyan takip süresi 26 ay (aralık: 1-153) idi ve 55 hasta (%77,5) öldü, 16 hasta (%22,5) hayattaydı. Altmış altı (%93) hastaya plevral MM, 5 hastaya (%7) peritoneal MM tanısı konuldu ve hastaların 18'inin (%25,4) Sarıhıdır, Karain ve Tuzköy'de ikamet ettiği karar verildi. Ortanca OS plevral MM için 16 ay (aralık: 1-133) ve peritoneal MM için 21 ay (aralık: 9-117) idi. Tanı anında 60 yaş ve altındaki hastalarda anlamlı olarak daha yüksek OS gözlendi (p=0,014). Nevşehir Hastanesi'nde sadece 6 hasta (%8,5) ve Kapadokya dışında 65 hastanın %91,5'i teşhis edildi.

**Sonuç:** Çalışmamızda Kapadokya'daki güncel durum değerlendirilmiştir. MM hastalarının OS son 30 yılda önemli ölçüde değişmemiştir. Hastaların yaklaşık %90'ı tanı ve tedavi için il dışına çıkmak zorunda kalmıştır. Bölgedeki mevcut durumu ve tedavi sonuçlarını değerlendirmek için ek araştırmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Kapadokya, malign plevral mezotelyoma, malign peritoneal mezotelyoma

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## Introduction

Malignant mesothelioma (MM) is a rare progressive fatal malignant tumour associated with asbestos (1). The median age of diagnosis is 74 years. MM is twice more frequent in males than in females due to the occupational exposure. The latent period from asbestos exposure to MM development is approximately 20-40 years (2,3). The overall survival (OS) is poor (4-6). The most effective method for preventing MM is to avoid its risk factors (6,7).

Cappadocia is one of the most common places where MM has been observed worldwide (5,6). This situation first emerged in 1975 with the individual efforts and self-sacrificing research of Baris et al. (8-10). A national mesothelioma registry unit is not available in Turkey. In 2015, the Ministry of Health's Cancer Control Department published the cancer statistics. According to these statistics, the incidence of age-standardised mesothelioma has been reported as 1.1/100.000 in males and 0.6/100.000 in females. There is no separate title for the Cappadocia region in these statistics (5,11).

The first epidemiological studies of mesothelioma in Turkey were conducted in 1970 by Baris et al. (8,9). In these studies, the incidence of MM in the Karain village was found to be very high. In the detailed evaluation, the data of the Kayseri State Hospital, which is the closest hospital to Karain, was examined and we found that almost all of these patients were treated as Tuberculosis and all of them died within a year. In 1975, Baris and his colleagues examined the Karain village, which had a population of 800 at that time and the incidence of mesothelioma was 1000 times higher than in the other regions. Similar results were obtained in Tuzköy, which is 40 km away from Karain (5). It was observed that 50% of the deaths in Karain, Sarıhıdır and Tuzköy were caused by MM (12). In Karain (Female/Male) 76/74, Tuzköy 54/51 and Sarıhıdır, 7/8 deaths were found to be caused by MM (13). Due to these findings, it was decided to evacuate Tuzköy-Karain and Sarıhıdır.

In this study, the data of 8 state hospitals in Cappadocia, one of the places where MM is most common, were examined. It had as aim to provide information regarding the current situation of MM. Specifically, the study aimed to investigate the demographic characteristics, adequacy of diagnosis and treatment facilities, OS and the factors affecting the OS of MM patients admitted to hospitals in the region.

## Methods

In this study, patients who were admitted to local public hospitals in Cappadocia between 01.01.2007 and 25.09.2019 were evaluated retrospectively as patients with pleural or peritoneal MM. Patient interview information, patient files, and the electronic system data were used for the study. Local hospitals whose data were extracted from the electronic system are Acigol District Integrated Hospital, Avanos District Integrated Hospital, Derinkuyu District Integrated Hospital, Gülşehir District Integrated Hospital, Hacibektas District Integrated Hospital, Urgup State Hospital, Nevşehir State Hospital, Kozakli Physical Therapy and Rehabilitation Hospital. The data of the patients admitted to these 8 hospitals in the Cappadocia region were reviewed retrospectively. The study was conducted in accordance with the Helsinki Declaration and it was approved by the Ethics Committee of Nevşehir Governorship Provincial Health Directorate in September 2019 (approval number: 26171210-020). Informed consent was obtained from all the patients or relatives (for exitus patients) before the analysis.

Demographic status of the patients, centre of MM diagnosis, access to treatment and the latest status were noted. The study included adult patients between the stages of 1 and 4 according to AJCC-8, who were undergoing curative/palliative treatment and had complete information. Patients whose pathology report details were not available and missing file and follow-up information were excluded from the study.

The primary endpoint of the study was the OS. The date of diagnosis was accepted as the starting date for the OS. The final check-in date for patients experiencing an OS endpoint is the exitus date for ex-patients. Most of the patients could not be diagnosed and treated in Cappadocia. The treatment details were not available in these patients' files data and electronic system. Therefore, the progression free survival (PFS) could not be calculated. The secondary endpoint of the study was to evaluate the current status of MM cases in Cappadocia and to determine the patients' access to diagnosis/treatment.

### Statistical Analysis

SPSS ver. 24 was used in this study. The normality of the variables was evaluated using visual and analysis methods and non-parametric tests were used since the variables did not fit the normal distribution. Chi-square and Fisher's exact tests were used to determine the differences in the demographic characteristics of the patients. Spierman's rank correlation test was used for univariate correlation analysis. Kaplan-Meirer was used for univariate survival analysis and the log rank test was also used. In the multivariate analyses, Cox Regression test was used. Statistical significance was accepted as less than 0.05.

## Results

We evaluated 1497 medical record (It is not the number of patients- It is the number of entered diagnosis of mesothelioma into the electronic system). Only 71 patients who met the inclusion criteria were identified. These 71 patients were treated with curative/palliative treatment in the 8 different state hospitals in the Cappadocia region with the diagnosis of stage 1-4 MM between 01.01.2007 and 25.9.2019 retrospectively. The median follow-up period was 26 (range: 1-153) months. During the follow-up period, 55 patients (77.5%) were ex and 16 patients (22.5%) were alive. In our study, 39 patients (54.9%) were females and 32 patients (45.1%) were males. The median age of the patients at the time of diagnosis was 66 (range: 36-86) the years. There was only one patient who was under 45 years of age at the time of diagnosis. This patient was diagnosed with malignant pleural mesothelioma at the age of 36 and he is currently residing in Tuzköy. Sixty-six (93%) patients were diagnosed with malignant pleural mesothelioma and 5 (7%) patients with malignant peritoneal mesothelioma.

Only 6 patients (8.5%) were diagnosed at Nevşehir Public Hospital. MM (91.5%) of 65 patients were diagnosed outside Cappadoccia. Only 9 patients (12.7%) received supportive treatment for curative purposes and 62 patients (87.3%) received palliative support. Symptoms of patients admitted to the regional hospitals; 28 patients (39.4%) had dyspnoea,

18 patients (25.3%) had general condition disorder, 10 patients (14.1%) had pain, 4 patients (5.6%) had acute renal failure, 4 patients (5.6%) had hypertension, 2 patients (5.6%) 2.8% were admitted to psychiatry clinic with depression and 2 patients (2.8%) presented with neurological findings (1 seizure + 1 speech disorder). The stages of the patients at the time of admission to the hospital (not the moment of diagnosis); 6 (8.5%) were operable, 55 (77.4%) were inoperable and 10 (8.5%) were metastatic. Thoracentesis was performed in 8 (11.3%) patients, while paracentesis was performed in 13 (18.3%) patients. In the Nevşehir Public Hospital, computer tomography (19.7%) was administered to 14 patients, of which 9 (12.7%) were curative. There were no oncology clinics in the other 7 hospitals. Besides, there is no radiotherapy centre in Cappadocia.

When the patients were examined in terms of their place of residence, 21 patients (29.6%) were examined in Urgup (Karain and Sarıhıdır were not included) and nineteen patients (26.8%) in Gülşehir (Tuzköy were not included). It was observed that 18 (25.4%) of the patients were residing in Sarıhıdır, Karain and Tuzköy with the decision of evacuation, but not completely separated (2 patients resided in Karain, 6 patients were residing in Sarıhır, 10 patients were still residing in Tuzköy) (Figure 1). Patient data are summarised in Table 1.

Another remarkable rate was the need for psychiatric support. The 26 (37.1%) patients received medical treatment for depression and anxiety.

Median OS was 16 months (range: 1-133) for pleural MM and 21 months (range: 9-117) for peritoneal MM. The OS difference between pleural MM and peritoneal MM was not statistically significant (p=0.23). The one-year OS for pleural MM was 60.9% and the 2-year OS was 31%. For peritoneal MM, the one-year OS is 60% and 2-year OS is 40% (Figure 2).

There were 7 patients with a survival of more than 5 years. The survival of these patients were 133 months (pleural MM), 117 months (peritoneal MM), 115 months (pleural MM), 101 months (pleural MM), 96 months (pleural MM), 87 months (peritoneal MM) and 86 months (pleural MM) months. For pleural MM, gender (p=0.89), right or left pleural disease (p=0.84), diagnosis and treatment (p=0.38) being performed outside or within the province and patients still living in Tuzköy-Sarıhıdır-Karain (p=0.33) did not significantly affect OS (Figure 3).

The relationship between pleural MM OS and age at diagnosis was investigated. The median OS value of patients aged 60 years or less at the time of diagnosis was 23.9 (range: 4-133), whereas the median OS value of patients over 60 years of age was 13.4 (range: 1-117) (p=0.014) (Figure 4).

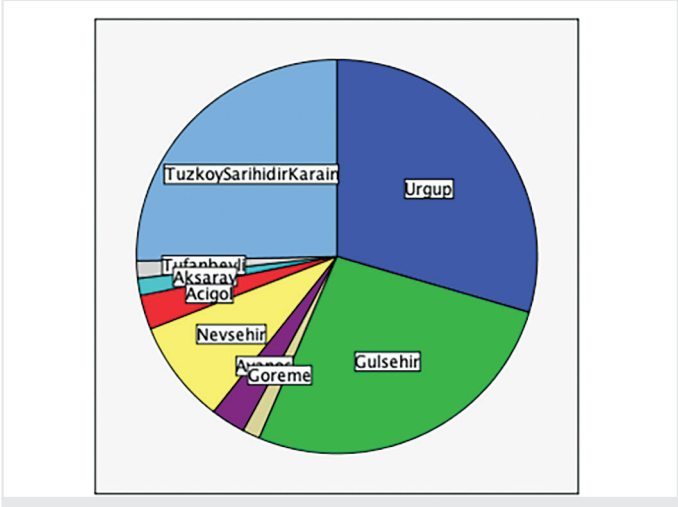


**Figure 1.** Centres where the patients resided at the time of admission

## Discussion

In the current study, 71 MM patients who were admitted to 8 different hospitals in Cappadocia in the last 12 years were identified. Sixty-six (93%) of them had a pleural origin and 5 (7%) had a peritoneal origin. Median OS was 16 months for pleural MM and 21 months for peritoneal MM. The OS of the patients included in our study was only adversely affected by advanced age. The gender, pleural or peritoneal origin, right and left lung location, diagnosis and treatment in-province or out-of-province and residing in high-risk endemic regions did not significantly

**Table 1. Patient details**

| | | |
|---|---|---|
| Gender | Female | 39 (54.9%) |
| | Male | 32 (45.1%) |
| Primer | Malignant pleural mesothelioma | 66 (90%) |
| | Malignant peritoneal mesothelioma | 5 (7%) |
| Treatment | Curative | 9 (12.7%) |
| | Palliative | 62 (87.3%) |
| Symptoms | Dyspnoea | 28 (39.4%) |
| | General condition disorder | 18 (25.3%) |
| | Pain | 10 (14.1%) |
| | Acute renal failure | 4 (5.6%) |
| | HT | 4 (5.6%) |
| | Depression | 2 (2.8%) |
| | Neurologic finding | 2 (2.8%) |
| Residence | Sarıhıdır | 6 (8.4%) |
| | Tuzköy | 10 (14.1%) |
| | Karain | 2 (2.8%) |
| | Ürgüp | 21(29.1%) |
| | Gülşehir | 19 (26.8%) |
| | Nevşehir (Centre) | 6 (8.5%) |
| | Avanos | 2 (2.8%) |
| | Acıgöl | 2 (2.8%) |
| | Aksaray | 1 (1.4%) |
| | Tufanbeyli | 1 (1.4%) |
| Diagnosis | In Cappadoccia | 6 (8.5%) |
| | Outer centre | 65 (91.5%) |
| Stage | Operable | 6 (8.5%) |
| | In-operable | 55 (77.4%) |
| | Metastatic | 10 (14.1%) |
| Last status | Ex | 55 (77.5%) |
| | Alive | 16 (22.5%) |

HT: Hypertension

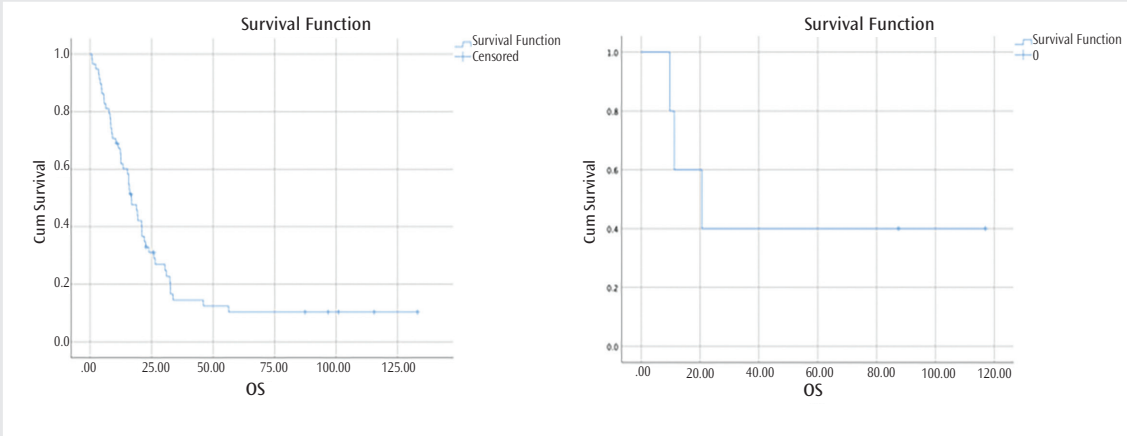


**Figure 2.** Overall survival analysis of patients with malignant pleural mesothelioma and malignant peritoneal mesothelioma, respectively

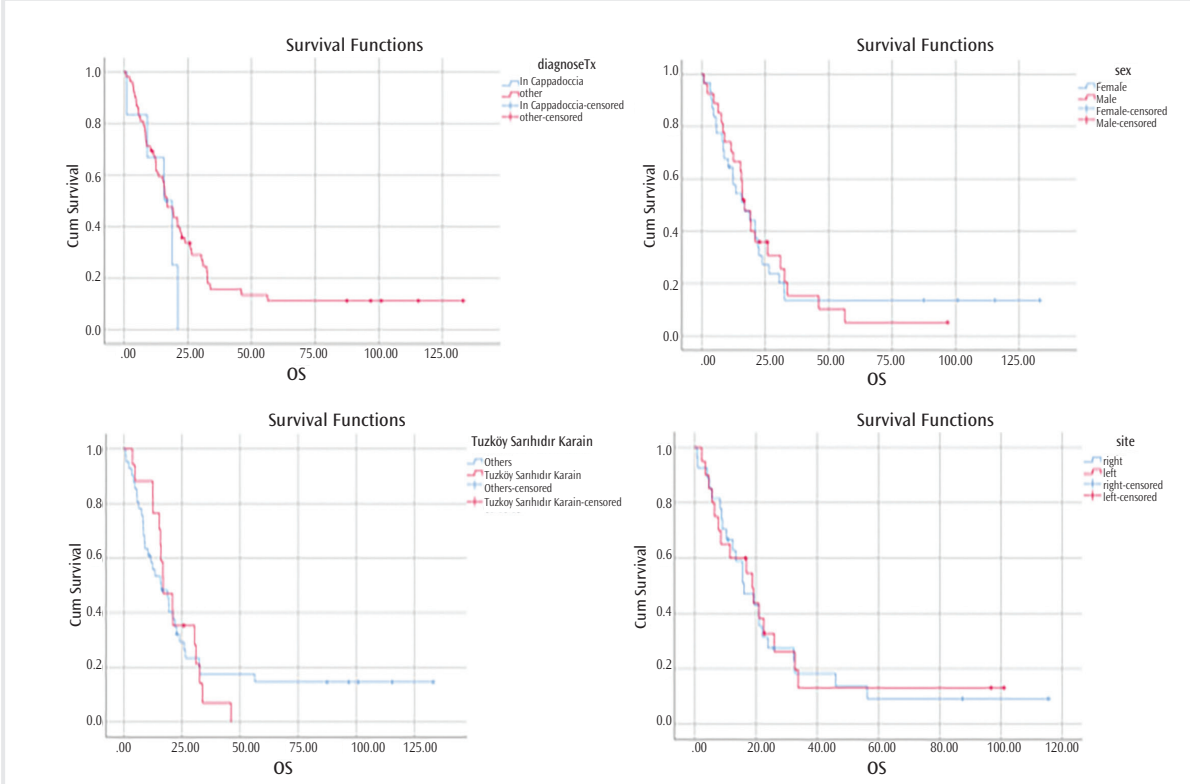


**Figure 3.** Detailed analysis of variables with pleural MM and OS

MM: Malignant mesothelioma, OS: overall survival

affect OS. When evaluated in terms of access to health services, 90% of the patients could not have been diagnosed or treated in Cappadocia. Palliative treatment is the only available facility in the region.

The median OS of the patients were 16 months for pleural MM and 21 months for peritoneal MM. Baris (14) evaluated 185 MM patients in 1980 and determined the period from onset of symptoms to death as approximately 18 months. Selçuk et al. (15) evaluated 135 pleural MM patients in 1992. In their evaluation, the median OS was found to be 13.5 months for erionitis-related MM and 21.5 months for MM associated with other asbestos dust. Although the patients in the diagnosis stages of our study do not know the treatments they receive in detail, it is seen that patients' OS has not changed dramatically in the last 40 years.

It has been reported in the literature that MM is more common in men (3,5). In this study, 39 (54.9%) of the patients were females and 32 (45.4%) were males. This data is not consistent with the literature, but it is consistent with the first study conducted in Cappadocia (5). In addition, male gender was defined as a negative prognostic factor (16-18). In the SEER analysis of 14,228 diseases published by Taioli et al. (3) in 2014, the OS of women was reported to be 3 times higher than that of men. In the current study, no significant effect of gender on OS was observed. In this

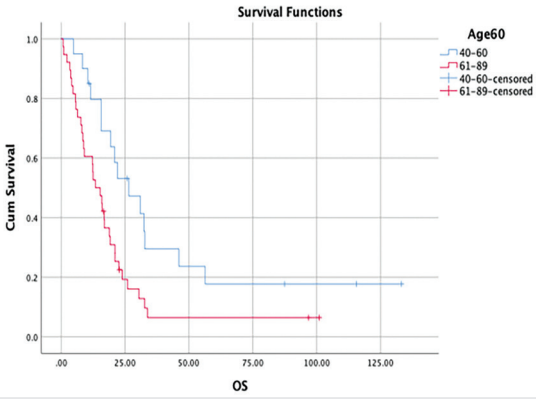


**Figure 4.** Relationship between patient age and OS in pleural MM

MM: Malignant mesothelioma, OS: overall survival

**Figure 5.** The area to the right of Kızılırmak is the old Sarıhıdır. The area on the left is the new settlement

state, this data are consistent with the retrospective study of Koyuncu et al. (19), which evaluated 60 patients with MM.

In case of intensive exposure, MM develops at an earlier age (20). In the preliminary cross-sectional studies in Cappadocia, it has been reported that there are MM patients in their 20s (5). In our study, there was one case diagnosed under the age of 40 and this case has lived in Tuzköy. Also, there were 5 cases under 50 years of age. In many studies, advanced age has been defined as a poor prognostic factor (16-18). In our study, lower OS was obtained in elderly patients.

Peritoneal Mesothelioma constitutes 7%-30% of all MM cases (8). It has been reported that peritoneal MM has better survival than pleural MM (17). In this study, peritoneal mesothelioma accounted for 7% of cases. Median OS of patients with pleural MM was 16 months (range: 1-133), while the median survival of patients with peritoneal MM was 21 (range: 9-117) (p=0.23). In addition, 2 (28.5%) of 7 patients with OS values greater than 5 years were diagnosed with peritoneal MM and these 2 patients are still alive. Although peritoneal MM patients had higher median survival and OS status higher than 5 years, the difference between pleural MM was not significant. This result may be due to the small number of peritoneal MM patients.

Another issue we want to consider is the access to health services for patients and the evaluation of the current cases of MM. As it is known, Cappadocia is an endemic MM region. When the endemic MM cases were examined, no high incidence was observed in any region as much as in Cappadocia (5,7). For example, endemic mesothelioma was reported in the Sicilian region of Italy between 1980 and 1997 due to the Etna Volcanic Mountain and the total number of cases in this region was 17 (10 men, 7 women). The population of the region is 23.000 for that period (21). Due to serpentine-coated roads, an increase in MM cases was reported in Kaleonia and 109 cases were observed between 1984 and 2008 (22). In Cappadocia, 50% of deaths in high-risk areas have been reported to be caused by MM (5).

This endemic MM was identified as zeolite stones used in house construction in these three villages (13). The villages were evacuated to prevent asbestos exposure and to reduce MM cases. There are currently three problems in this regard. First, the high-risk areas are not fully evacuated. It was found that 18 of 71 patients in our study still live in Karain-Tuzköy and Sarıhıdır. They are still inhabitants of these villages. Secondly, erionite was found not only in the stones of the houses, but also in the air of these villages (23). Small amounts of erionite inhalation may be sufficient for MM development. For example, in an animal experiment in rats, MM developed in 27 out of 28 rats inhaling erionite; MM developed in 11 of 648 rats in other asbestos types (24). It is located very close to the new settlements - the old ones (Figure 5). Some of the inhabitants of Tuzköy-Karain and Sarıhıdır have evacuated their houses and moved to the new settlement. However, since the newly settled houses are close to the old ones, the extent of exposure due to increased erionite detected in the air continues and the current status of MM incidence should be examined separately. The third situation is the long latent period between asbestos exposure and MM development. Long-term follow-up of patients is required even if the sites are evacuated. Data on families migrating to Europe are available in the literature. In a study conducted in Sweden, it was found that increasing cases of malignant pleural mesothelioma (MPM) originate from families migrating from the Karain. The incidence of MPM was 639/100,000 per year for males and 1,267/100,000 per year for females. In this group, the mortality rate caused by MPM was 78%. These rates are compared with the Swedish population; 135.5 times for men and 1336.3 times higher for women (25). However, there is insufficient data on the final status of people moving out of Cappadocia in Turkey.

The development of MM is not only related to exposure to asbestos, but also individual carcinogenesis susceptibility (7,13,26). In the analysis of workers exposed to crocidolite asbestos in South Africa, 4.6% of them exitus due to MM. Increased exposure is a risk factor for the development of MM, but some of the exposed patients have no disease (10). Dogan et al. (27) reported in 2006 that these endemic and dense MM cases seen in Cappadocia were not only caused by erionite, but also by genetic predisposition. In a study conducted in Karain, the last 6 generations of the patients were examined and it was argued that autosomal dominant mechanisms could play a role. Another case that supports this issue is that, there is a relatively low rate of MM cases in Karlık village (where erionite is detected) which is 4 km away from Karain (28). Therefore, further studies are needed to determine the extent to which

the incidence of MM decreases with reduced asbestos exposure and to what extent genetic predisposition is effective in this endemic.

There are a limited number of articles describing the current state of the literature in Cappadocia. There is a need for studies on the effectiveness of the measures taken and the treatment and response situations. The reason for this limitation is that patients are still unable to receive treatment in their provinces and they are distributed to different centres such as İstanbul, Ankara, Kayseri or Europe in accordance with their social support. This is an important challenge that reveals the current status of MPM in Cappadocia, the effectiveness of the treatments applied and the latest status of patients. Evaluation of the patients in one easy-to-reach centre may benefit the patient. In addition, sharing results from this region with the highest incidence of this rare disease worldwide will contribute to the literature. For example, Carbone et al. (13), in our region as a result of research, the first mineral fibre carcinogenesis modulating gene could be identified: BAP-1, in the early 2000s (5,6).

There are some important limitations of our study. First of all, the study is retrospective. The stages of diagnosis, treatment details and response to treatment are unknown. Only patients whose pathology report was available were included in the study, and treatment details were not noted in detail in many files. Therefore, PFS could not be calculated. However, our study covers all state hospitals in Cappadocia. We think that the data obtained by examining the records of 8 different hospitals in the region can give an idea regarding the current situation in Cappadocia.

## Conclusion

The OS of MM patients has not changed dramatically in the last 30 years. Approximately 90% of patients had to go out of the province for diagnosis and treatment. Additional studies are needed to evaluate the current situation and treatment results in the region.

**Acknowledgment**

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**Ethics**

**Ethics Committee Approval:** The study was conducted in accordance with the Helsinki Declaration and it was approved by the Ethics Committee of Nevşehir Governorship Provincial Health Directorate in September 2019 (approval number: 26171210-020).

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

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

**Authorship Contributions:** Surgical and Medical Practices - İ.P.A., M.B.; Concept - İ.P.A., S.A.A.; Design - İ.P.A.; Data Collection or Processing - İ.P.A.; Analysis or Interpretation - M.B., S.A.A.; Literature Search - İ.P.A., M.B., S.A.A.; Writing - İ.P.A.

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

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## References

1. Kim J, Bhagwandin S, Labow DM. Malignant peritoneal mesothelioma: a review. Ann Transl Med 2017; 5: 236.
2. Bibby AC, Tsim S, Kanellakis N, Ball H, Talbot DC, Blyth KG, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev 2016; 25: 472-86.
3. Taioli E, Wolf AS, Camacho-Rivera M, Flores RM. Women with malignant pleural mesothelioma have a threefold better survival rate than men. Ann Thorac Surg 2014; 98: 1020-4.
4. Robinson BW, Musk AW, Lake RA. Malignant mesothelioma. The Lancet 2005; 366: 397-408.
5. Salih Emri. The Cappadocia mesothelioma epidemic: its influence in Turkey and abroad. Ann Transl Med 2017; 5: 239.
6. Carbone M, Kanodia S, Chao A. Consensus Report of the 2015 Weinman International Conference on Mesothelioma. J Thorac Oncol 2016; 11: 1246-62.
7. Metintas M, Hillerdal G, Metintas S, Dumortier P. Endemic malignant mesothelioma: exposure to erionite is more important than genetic factors. Arch Environ Occup Health 2010; 65: 86-93.
8. Baris YI, Sahin AA, Ozesmi M. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Urgüp in Anatolia. Thorax 1978; 33: 181-92.
9. Baris I, Artvinli M, Sahin A, Savas T, Erkan ML. [Occurrence of pleural mesothelioma. Chronic fibrosing pleurisy and calcified pleural plaques in Turkey in relation with environmental pollution by mineral fibers (author's transl)]. Rev Fr Mal Respir 1979; 7: 687-94.
10. Artvinli M, Bariş YI. Malignant mesotheliomas in a small village in the Anatolian region of Turkey: an epidemiologic study. J Natl Cancer Inst 1979; 63: 17-22.
11. TÜİK. "Ölüm Nedeni İstatistikleri, 2014". last accessed date: 16.01.2017. Available from: http://www.tuik.gov.tr/PreHaberBultenleri.do?id=18855
12. Bariş B, Demir AU, Shehu V, Kisacik G, Bariş YI. Environmental fibrous zeolite (erionite) exposure and malignant tumors other than mesothelioma. J Environ Pathol Toxicol Oncol 1996; 15: 183-9.
13. Carbone M, Emri S, Dogan AU, Steele I, Tuncer M, Pass HI, et al. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. Nat Rev Cancer 2007; 7: 147-54.
14. Baris Y. The clinical and radiological aspects of 185 cases of malignant pleural mesothelioma. IARC Sci Publ 1980; 30: 937-47.
15. Selçuk ZT, Cöplü L, Emri S, Kalyoncu AF, Sahin AA, Bariş YI. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey. Analysis of 135 cases. Chest 1992; 102: 790-6.
16. Moore AJ, Parker RJ, Wiggins J. Malignant mesothelioma. Orphanet J Rare Dis 2008; 3: 34.
17. Amin W, Linkov F, Landsittel DP, Silverstein JC, Bashara W, Gaudioso, et al. Factors influencing malignant mesothelioma survival: a retrospective review of the National Mesothelioma Virtual Bank cohort. F1000 Res 2018; 7: 1184.
18. Taioli E, Wolf AS, Camacho-Rivera M, Kaufman A, Lee DS, Nicastri D, et al. Determinants of Survival in Malignant Pleural Mesothelioma: Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients. PLoS One 2015; 10: e0145039.

19. Koyuncu A, Koksal D, Ozmen O, Demirag F, Bayiz H, Aydogdu K, et al. Prognostic factors in malignant pleural mesothelioma: a retrospective study of 60 Turkish patients. J Cancer Res Ther 2015; 11: 216-22.

20. Dragani TA, Colombo F, Pavlisko EN, Roggli VL. Malignant mesothelioma diagnosed at a younger age is associated with heavier asbestos exposure. Carcinogenesis 2018; 39: 1151-6.

21. Soffritti M, Minardi F, Bua L. First experimental evidence of peritoneal and pleural mesotheliomas induced by fluoro-edenite fibres present in Etnean volcanic material from Biancavilla (Sicily, Italy). Eur J Oncol 2004; 9: 169-75.

22. Baumann F, Maurizot P, Mangeas M, Ambrosi JP, Douwes J, Robineau B. Pleural mesothelioma in New Caledonia: associations with environmental risk factors. Environ Health Perspect 2011; 119: 695-700.

23. Sluis-Kremer GK. Asbestos disease at low exposure after long residence times. Ann. NY Acad Sci 1991; 643: 182-93.

24. Wagner JC Skidmore JW, Hill RJ, Griffiths DM. Erionite exposure and mesotheliomas in rats. Br J Cancer 1985; 51: 727-30.

25. Metintas M, Hillerdal G, Metintas S. Malignant mesothelioma due to environmental ex- posure to erionite: follow-up of a Turkish emigrant cohort. Eur Respir J 1999; 13: 523-6.

26. Roushdy-Hammady I, Siegel J, Emri S, Testa JR, Carbone M. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 2001; 357:444-5.

27. Dogan AU, Baris YI, Dogan M, Emri S, Steele I, Elmishad AG, et al. Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey. Cancer Res 2006; 66: 5063-8.

28. Metintas M, Hillerdal G, Metintas S, Dumortier P. Endemic malignant mesothelioma: exposure to erionite is more important than genetic factors. Arch Environ Occup Health 2010; 65: 86-93.

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# Intraoperative Neurophysiology Practice in the Surgical Treatment of Posterior Fossa Lesions: Cerrahpaşa Experience

## Posterior Fossa Lezyonlarının Cerrahi Tedavisinde İntraoperatif Nörofizyoloji Uygulamaları: Cerrahpaşa Deneyimi

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## ABSTRACT

**Introduction:** Posterior fossa surgery involves a risk of injury on a variety of critical neurological structures. Intraoperative neuromonitoring (IONM) has become a routine scrutiny with newly developed tests for sparing these structures. This present study aims to evaluate the IONM experience in posterior fossa surgery of a tertiery neurosurgical centre.

**Methods:** Forty-five patients (26 females, 19 males; age between 2 and 72 years) who underwent surgery for different posterior fossa pathologies from 2016 to 2019 were retrospectively evaluated.

**Results:** Six and thirteen patients experienced extremity motor evoked potential (MEP) and somatosensory evoked potential changes respectively. Brainstem auditory evoked potential changes were seen in four patients. Corticobulber MEP (CoMEP) of facial nerve deteriorated in seven patients. All new onset neurological deficits of cranial nerves or long tracts were concordant with IONM findings except for one patient who developed 6$^{th}$ nerve palsy without CoMEP findings. Loss of neurological function immediately after surgery was observed in 13 patients while permanent evident neurological worsening occurred in five patients.

**Conclusion:** IONM is an indispensable component of the skull base surgery. Comprehensive multimodality monitoring provides a real-time, complete assessment of critical neurological structures, facilitates safer and more aggressive management and thus improves quality of life.

**Keywords:** Blink reflex, brainstem auditory evoked potential, corticobulber motor evoked potential, multimodality, neuromonitoring, posterior fossa lesions, skull base surgery

## ÖZ

**Amaç:** Posterior fossa lezyonlarının cerrahi tedavisi, çeşitli kritik nörolojik yapılarda yaralanma riski içerir. İntraoperatif nöromonitörizasyon (İONM), yeni geliştirilen yöntemler sayesinde bu yapıları korumak için rutin bir inceleme haline gelmiştir. Bu çalışma, üçüncü basamak bir nöroşirürji merkezinin posterior fossa cerrahisinde İONM deneyimini değerlendirmeyi amaçlamaktadır.

**Yöntemler:** 2016-2019 yılları arasında farklı posterior fossa patolojileri için ameliyat edilen 45 hasta (26 kadın, 19 erkek; 2 ila 72 yıl) retrospektif olarak incelendi.

**Bulgular:** Sırasıyla altı ve 13 hastada, ekstremite motor uyarılmış potansiyeli (MEP) ve somatosensoriyel uyarılmış potansiyel değişiklikleri meydana geldi. Dört hastada beyin sapı işitsel uyarılmış potansiyel değişiklikleri görüldü. Fasiyal sinirin kortikobulber MEP (CoMEP) 7 hastada kötüleşti. Kraniyal sinirlerin veya uzun traktların tüm yeni başlayan nörolojik defisitleri, CoMEP bulguları olmaksızın 6. sinir felci gelişen bir hasta dışında, İONM bulguları ile uyumlu idi. Ameliyattan hemen sonra nörolojik fonksiyon kaybı 13 hastada gözlenirken, bunlardan beşinde belirgin düzeyde kalıcı nörolojik kötüleşme meydana geldi.

**Sonuç:** İONM kafa tabanı cerrahisinin vazgeçilmez bir bileşenidir. Kapsamlı çok modlu İONM, kritik nörolojik yapıların gerçek zamanlı, eksiksiz bir değerlendirmesini sağlar ve daha güvenli ve daha agresif bir tedavi yönetimini mümkün kılarak yaşam kalitesini yükseltir.

**Anahtar Kelimeler:** Göz kırpma refleksi, beyin sapı işitsel uyarılmış potansiyel, kortikobulber motor uyarılmış potansiyel, çok modlu, nöromonitorizasyon, posterior fossa lezyonları, kafa tabanı ameliyatı

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## Introduction

Cranial base surgery aims to provide an optimal treatment for pathology with minimal or no neurological deficit in order to protect the quality of life. Intraoperative neurophysiologic monitoring (IONM) has become an imperative component of skull base surgery to avoid unobtrusive maneuvers that can result in the injury of delicate nuclei, tracts, or nerves and thus a hazardous neurologic injury (1,2).

The posterior cranial fossa is the largest of the 3 cranial fossae and contains a complex anatomy of vascular and neuronal structures, which include 10 of 12 pairs of cranial nerves (CN), long tracts of motor activities and sensory pathways and centres for controlling balance and regulating consciousness (3). Therefore, IONM for posterior fossa surgery consists of long tracts monitoring, several CN mapping and monitoring and also brainstem reflex tests, which has been developed recently to evaluate the integrity of brainstem structures (4-7). However, there is no single test that incorporates all of them. Therefore, IONM of skull base surgery is a multimodality concept that necessitates the use of a number of modalities complementing each other simultaneously in order to evaluate the integrity of neurologic structures.

This article reports the clinical and physiological outcomes achieved in posterior fossa surgeries accompanied by IONM in a tertiary referral hospital.

## Methods

### Ethical Approval

The study was conducted with the approval of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethical Committee (reference no: 2020/70721) in concordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients.

### Patient Population

Forty-five patients (26 females, 19 males; mean 41.2 years; 2-72 years) who underwent surgery for a variety of posterior fossa pathologies accompanied with IONM from March 2016 to May 2019 were retrospectively evaluated. Demographic information, surgical resection rates, pathology, IONM modalities, techniques, electrophysiological findings and neurologic examination were evaluated.

All the patients reported in this series were informed preoperatively about the IOMN application, since the IOMN procedure is already a well described and approved technique. Due to the retrospective nature of this study, patient consent was not sought.

### Intraoperative Neuromonitoring

Mapping and monitoring techniques were utilised for intraoperative neurophysiology. Mapping identified CNs and their nuclei, and monitoring continuously assessed the functional integrity of the pathways and reflex circuits. All the recordings, stimulation and data processing were performed using Cadwell elite IONM system by a clinical neurophysiologist (E.T.) certified for intraoperative neuromonitoring by the International Society of Intraoperative Neurophysiology.

Standardised institutional setup was used. Recording muscles were determined according to the lesion's location and surgical approach. The stainless steel needle electrodes (13-19 mm, Xi'an friendship medical company) were used to record the muscle responses for motor evoked potentials (MEPs) and electromyography (EMG) as well as to stimulate the peripheral nerves for somatosensory evoked potential (SEP). Disposable corkscrew electrodes were used for the stimulation of MEPs and also for the recording of cortical SEPs. SEPs were obtained by stimulating the median or ulnar nerves and recording cortically with an electrode montage of C3'-Fz/C4'-Fz or C3'-C4'/ C4'- C3', while the lower extremities' SEPs were obtained by stimulating the posterior tibial nerves recording from cortical Cz'-Fz and C3'-CZ'/C4-CZ'. These SEPs monitored the sensory pathway. SEP recordings were set up with a sensitivity of 0.5-1 µV/mm and a sweep speed of 100 msec; filter settings were set to 30-700 Hz; the stimulus frequency was 1.7-4.71 Hz and the stimulation duration was 200-300 µs for the median/ulnar nerve and 300-500 µs for the tibial nerve. The mean stimulus intensity was 15-20 and 30-40 mA for median/ulnar and tibial nerves, respectively.

The corticospinal motor system was evaluated with extremity MEPs, which were obtained by stimulating the motor cortex transcranially (C1/C2 for right MEP, C2/C1 for left) and recording from the lower and upper extremities (if we could not get responses from this montage, we used the C3/C4). Corticobulber motor evoked potential (CoMEP) for muscles innervated by the CNs was obtained using C3-Cz or C4-Cz montages (according to the international 10-20 system for electroencephalogram) by activating the corticobulber tract. MEP responses were recorded from the appropriate muscles contralateral to the lesion location. Multipulse stimulation consisting of 5-6 pulses of 0.5 ms duration with an interstimulus interval (ISI) of 3-4 ms was used for MEPs. Stimulation intensities varied between 100-600 V according to the individual. For recording CoMEPs, we used a short train consisting of 4 or 5 stimuli each with durations of 0.5 ms, seperated by an ISI of 1.5 and an intensity typically from 50-250 V. Simultaneously, we opened a different window for excluding peripheral responses in CoMEP. We applied a single stimulus to the same electrodes at 90 ms after delivering a short train of stimuli in order to exclude distal CN excitation by the absence of single pulse responses as described by Dong et al. (8).

CN mapping was achieved using a monopolar or bipolar hand-held stimulating electrode to find regions of the tumour that are not associated with the nervous system and identify CN trajectories. Mapping of CN motor nuclei, in case of necessity, was used for the surgical planning and the safe surgery to the brainstem. CN monitoring was provided with EMG and CoMEP.

Brainstem auditory evoked potential (BAEP) reflecting neuronal activity in the auditory nerve, cochlear nucleus, superior olive and inferior colliculus of the brainstem was obtained by stimulating with click stimuli from disposible foam ear tips and recording from A1/A2 electrodes placed ear lobe and cortical electrode CZ.

Blink reflex (BR), which is one of the brainstem reflexes, was performed bilaterally as a monitoring tool for brainstem reflexes, evaluating trigeminal afferents, brainstem connections between the trigeminal and facial nuclei and the facial nerve. We applied 1 to 5 rectangular constant-current stimuli with an ISI of 2 ms, an intensity of 20-60 mA and a train repetition rate of 0.4 Hz over the supraorbital nerve as described by Deletis et al. (9).

Monitoring was started immediately after anaesthesia induction and continued until the termination of the surgical procedure, as recommended by the American Clinical Neurophysiology Society in 2009 (10). All surgical procedures were followed on the visual screen in the operating room during surgery.

### Anaesthesia

Total intravenous anaesthesia consisting of propofol (1.5-2 mg/kg for anaesthesia induction and 6-10 mg/kg/h for maintenance) plus remifentanil (0.15 µg/kg/min) was used in all the patients. A short half-life muscle relaxant (rocuronium, 0.5 mg/kg) was used only during the time of tracheal intubation. We avoided the use of volatile anaesthetics since they reduce the MEP amplitude significantly compared to propofol (11,12). A bite block was placed to prevent tongue injuries during the intraoperative MEP monitoring.

### Warning Criteria for Intraoperative Neurophysiologic Changes

Reproducible cortical peak-to-peak amplitude decrements of more than 50% or 10% increases in the latency of the primary SEP cortical response (N20, P37) was considered a significant surgical event that is a cause for concern and heightened vigilance and/or should be intervened. These parameters have been summarised in a position statement by the American Society of Neurophysiological Monitoring (2).

The surgeon was informed as soon as any neurophysiologic change occurred, even if the warning criteria has not been fulfilled. However, a true warning event was decided only if changes were reproducible and continued to worsen in the following recordings.

Disappearance or consistent >50% MEP amplitude reduction when warranted by sufficient response stability, or amplitude reduction clearly exceeding variability when responses are less stable were considered significant warning signs. We did not use threshold criteria for MEPs and CoMEPs because of the lack of empirical evidence for constant voltage stimulation that was not documented.

Free-running EMG recording spontaneous muscle activity was observed for detecting surgically driven mechanical irritation and the possibility of damage of the CNs. In case spontanous activity was observed, surgery was interrupted and CoMEP was immediately repeated, along with continuous CoMEP measurements during the critical resection.

An amplitude decrement of more than 50% and an increase in latency of waves III and IV/V for more than 0.5 msec were considered critical in BAEP monitoring (13).

Disappearance was considered a significant warning criteria for BR during the surgery.

### Statistical Analysis

Data given in this study was analysed with IBM SPSS v23.0 (Chicago, USA). Only descriptive statistics were performed as this article does not include any inferential statistical data.

## Results

Demographic information of the patients, location of the pathology, surgical resection rates, persistant IONM changes and histopathological results are summarised in Table 1. IONM recordings of 45 patients were evaluated. CN mapping and monitoring of 3-12$^{th}$ CNs according to the tumour location, BAEP for 8$^{th}$ CN and brainstem monitoring, SEP for posterior cord and lemniscal system, MEPs for corticospinal and corticobulbar tractus monitoring were performed in all the patients.

**Table 1. Demografic data, extent of resection, location, hystopathological findings, preoperative and postoperative neurological examination and IONM findings of patients**

| Pt No | Age, gender | Pathology | Location | Excition | Preop examination | Early postop examination | Persistant ionm change |
|---|---|---|---|---|---|---|---|
| **New deficit group** | | | | | | | |
| 1 | 55, M | Ependymoma | Medulla | Grosstotal | Hemiparesis | Hemiplegia | MEP amplitude decrease |
| 2 | 23, F | Epidermoid | CPA | Grosstotal | HB1 | HB2 | BR threshold increase |
| 3 | 49, M | Epidermoid | CPA | Grosstotal | HB2 | HB3 | COMEP amplitude decrease 75% |
| 4 | 22, F | Epidermoid | CPA | Grosstotal | HB1 | HB2 | BR threshold increase |
| 5 | 21, F | Glioneuronal tumour | 4$^{th}$ ventricle | Grosstotal | BSF | Nystagmus | None |
| 6 | 42, M | Meningioma | Petroklival | Subtotal | BSF, HL | HB4 | COMEP amplitude decrease 70% |
| 7 | 28, M | Vestibular schwannoma | CPA | Grosstotal | BSF, HL | HB4 | COMEP amplitude decrease 65% |
| 8 | 67, M | Vestibular schwannoma | CPA | Subtotal | HL | HB5 | COMEP loss |
| 9 | 24, F | Vestibular schwannoma | CPA | Grosstotal | BSF, HL | HB3 | COMEP loss |
| 10 | 63, F | Vestibular schwannoma | CPA | Grosstotal | BSF, HL | HB5 | COMEP loss |
| 11 | 22, F | Vestibular schwannoma | CPA | Subtotal | HL | HB2 | COMEP amplitude decrease 64% |
| 12 | 23, F | Vestibular schwannoma | CPA | Subtotal | BSF, HL | HB2 | COMEP amplitude decrease 50% |
| 13 | 19, F | Vestibular schwannoma | CPA | Subtotal | HB1 | HB2 | COMEP morphological change |

**Table 1. contiuned**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **No new deficit group** | | | | | | | |
| 14 | 43, M | Anaplastik astrositoma | Cerebellum | Subtotal | Normal | No new deficit | BAEP change |
| 15 | 3, F | Anaplastik astrositoma | Cerebellum | Grosstotal | Vomiting | No new deficit | None |
| 16 | 30, M | Anaplastik pleomorphic xanthoastrocytoma | Medulla | Subtotal | BSF | No new deficit | SEP change |
| 17 | 12, M | Ependymoma | 4th ventricle | Grosstotal | BSF | No new deficit | None |
| 18 | 28, F | Ependymoma | 4th ventricle | Subtotal | BSF | No new deficit | None |
| 19 | 33, M | Ependymoma | Medulla | Subtotal | BSF | No new deficit | MEP amplitude decrease |
| 20 | 55, M | Epidermoid | CPA | Grosstotal | BSF, HL | HB1 | None |
| 21 | 43, F | Epidermoid | CPA | Grosstotal | Normal | HB1 | COMEP amplitude decrease 55% |
| 22 | 19, F | Epidermoid | CPA | Grosstotal | BSF, HL | HB1 | None |
| 23 | 66, F | Epidermoid | CPA | Subtotal | Normal | No new deficit | None |
| 24 | 33, M | Epidermoid | CPA | Grosstotal | BSF, HL | HB1 | None |
| 25 | 55, M | Epidermoid | CPA | Grosstotal | BSF | HB1 | None |
| 26 | 39, F | Ganglioglioma | Cerebellum | Subtotal | BSF | No new deficit | MEP and SEP amplitude decrease |
| 27 | 43, M | Hemangioblastoma | Medulla | Grosstotal | Normal | No new deficit | None |
| 28 | 9, M | Medulloblastoma | 4th ventricle | Grosstotal | Normal | HB1 | None |
| 29 | 9, F | Medulloblastoma | 4th ventricle | Grosstotal | BSF | No new deficit | COMEP loss |
| 30 | 52, F | Meningioma | CPA | Grosstotal | Normal | HB1 | None |
| 31 | 60, F | Meningioma | CPA | Grosstotal | Normal | HB1 | None |
| 32 | 38, F | Meningioma | Petroklival | Subtotal | Normal | HB1 | None |
| 33 | 55, F | Meningioma | Petroklival | Subtotal | BSF | HB1 | None |
| 34 | 62, F | Meningioma | Petroklival | Subtotal | BSF | HB1 | None |
| 35 | 44, F | Meningioma | Petroz apex | Subtotal | BSF | HB1 | None |
| 36 | 67, M | Meningioma | Petroz bone | Grosstotal | HL | HB1 | None |
| 37 | 32, F | Pilocytic astrocytoma | Medulla | Grosstotal | Normal | No new deficit | None |
| 38 | 25, F | Pilocytic astrocytoma | Cerebellum | Subtotal | BSF | No new deficit | None |
| 39 | 36, M | Vestibular schwannoma | CPA | Subtotal | HL | HB1 | None |
| 40 | 72, M | Vestibular schwannoma | CPA | Subtotal | BSF, HL | HB1 | SEP loss |
| 41 | 64, M | Vestibular schwannoma | CPA | Subtotal | HL | HB1 | SEP loss |
| 42 | 28, M | Vestibular schwannoma | CPA | Subtotal | Normal | HB1 | None |
| 43 | 38, F | Vestibular schwannoma | CPA | Grosstotal | BSF, HL | HB4 | None |
| 44 | 68, F | Vestibular schwannoma | CPA | Subtotal | BSF, HL | HB1 | None |
| 45 | 67, F | Vestibular schwannoma | CPA | Subtotal | HL | HB1 | None |

CPA: Cerebellopontine angle, BSF: brain stem finding, HL: Hearing loss, HB: House-Brackmann, COMEP: corticobulber motor evoked potential, MEP: motor evoked potential, IONM: intraoperative neuromonitoring, SEP: somatosensory evoked potential, M: male, F: female, BR: blink reflex, Pt: patients

Tumours in this series were located at the cerebellopontin angle (CPA) in 25 patients, petroclival region in 4, along petrous bone in 2, fourth ventricle in 5, cerebellar hemisphere in 4 and brainstem in 5.

Neurological deficits were present in 31 patients at the time of admission (Table 1). Clinical signs due to brain stem compression were manifested in 23 patients, while hearing loss in 17 patients was the second most common finding in our series. Facial nerve palsy was present in 3 patients during the preoperative period.

Histopathological diagnoses were vestibuler schwannoma in 14 patients, epidermoid in 9, meningioma in 8, ependimoma in 4, pilocytic astrocytoma in 2, anaplastic astrocytoma in 2, medulloblastoma in 2, pleomorphic xanthoastrocytoma in 1, hemangioblastoma in 1,

ganglioglioma in 1 and glioneuronal tumour in 1. Microscopic gross total resection and subtotal resections were achieved in 23 and 22 patients, respectively.

Immediate postoperative new neurologic deficit occurred in 13 patients. Preoperatively present hemiparesis of a patient with ependimoma of the medulla oblongata worsened due to hemiplegia. Another patient with a glioneuronal tumour located in the fourth ventricle developed right-sided 6th nerve palsy. The remaining 11 patients showed facial palsy of varying degree.

Neurological deficits of 4 patients, 1 with hemiplegia and 3 with facial palsy, returned to the initial neurological status before discharge, and in 2 other patients: 1 with facial palsy and 1 with 6th CN palsy, returned to normal at the last follow-up. At long term, disfiguring facial palsy (House-Brackmann scale 3 or above) was present in 5 patients and mild palsy (House-Brackmann scale 2) in 2.

Extremity MEP and SEP changes were seen in six and 13 patients, respectively. Of these, 3 patients in MEP and 5 in SEP met the warning criteria. However, only one patient having persistant MEP changes revealed postoperative new extremity deficit.

BAEP changes were present in four patients with lesions located in the 4th ventricle, which showed brainstem compression.

CoMEP of abducens, facial, glossopharyngeal and hypoglossal nerves were routinely applied to all the patients in this series. CoMEP of the 6th nerve did not show warning criteria in any patient. IONM of the 7th nerve revealed CoMEP changes in 17 patients. Six of 17 patients had amplitude decrement less than 50% or showed morphological changes, and 11 met the warning criteria (9 persistent and 2 transient). Of 9 patients showing persistent CoMEP changes, 7 had neurological worsening after the surgery.

BR was evaluated in 33 patients in this series. BR was lost in six patients and two patients with increased stimulation threshold that all came up with facial nerve deficit postoperatively.

## Discussion

The main objective of obtaining total resection in neurosurgical practice has been significantly changed over to sustaining the quality of life. IONM has been an indispensable tool to achieve this goal by facilitating to achievement of maximal resection while preserving vital structures. Use of IONM in neurosurgical procedures promoted a significant decrease of neurological complications from as high as 37% to less than 5% in some recent series (14,15).

Multimodality is essential during challenging surgical procedures since classical IONM methods such as SEP and BAEP allow to evaluate the neurological function in less than 20% of brainstem areas (16). To have a holistic understanding of CN and brainstem functioning, CN assessments such as CoMEP and brainstem reflexes such a BRs, and mapping by triggered EMG have been developed and found wide use (5,8,9,17).

This multimodality understanding proved to be useful in our series, since no patients who had a new postoperative neurological deficit showed prominent BAEP or SEP changes in this series. On the other hand, all patients, except one with postoperative 6th nerve palsy, showed some changes in at least one of the modalities during surgery.

In more than two-thirds of cases in this series, the facial nerve was at risk during surgery. More specifically, pathologies were located in CPA or along the petrous bone, which is adjacent to the cisternal segment of the facial nerve in 31 patients. Concordant to this, facial palsy was the most common postoperative new neurological deficit in this patient cohort. Facial nerve can be evaluated during surgery either via stimulation of the nerve where it exits from the brainstem with a hand-held probe (mapping) or with CoMEP (8,18). CoMEP monitors the functional integrity of the corticobulbar tracts arising from the cortex, passing through the cranial motor nuclei and terminating in the muscles innervated by CNs (8,19). Several advantages of CoMEP were described over mapping with a hand-held probe (8,11). First, defining the proximal part of the facial nerve and stimulating it in the presence of a large tumour may require extensive maneuvers that may damage the nerve. Second, CoMEP does not interrupt the course of the surgery, while mapping requires the surgeon to stop the surgical dissection. Third, CoMEP provides evaluation of the facial nerve entirely from its cortical origin to muscle terminations, while direct stimulation only assesses the facial nerve distal to the brainstem.

CoMEP was performed as part of a multimodal IONM setup in all cases in this series. CoMEP abnormalities were present in all the patients (11 patients) with postoperative new facial nerve deficit, while 8 showed the warning criteria, 2 amplitude decreament less than 50% and threshold increase in BR eliciting and 1 morphological change. Eight patients with warning criteria included all the 5 patients with disfiguring postoperative facial palsy, 2 patients who returned to the initial status and one had mild persistent facial palsy. Along 5 patients with disfiguring facial palsy, BR was lost in 4 of them at the end of the procedure and was not elicited in one patient at the baseline recording.

BR was recommended as a new tool to evaluate structures involved in the reflex arc, including trigeminal afferents, brainstem connections between the trigeminal and facial nuclei and the facial nerve (19). BR was found to have a strong correlation with facial and/or trigeminal CoMEPs during skull base surgery in 21 patients undergoing posterior fossa surgeries, with this being a predictor of clinical outcome (4). Our results also suggest that BR is a complementary tool to facial nerve CoMEPs to specifically determine the severity of facial nerve deficits, as all cases with permanent facial nerve deficits in our series showed BR abnormalities whether the CoMEP changes met the warning criteria or not. We also concluded that severe facial nerve palsy is concordant with CoMEP changes in more than one muscle group together with BR loss. Patients with new mild deficit or patients with improving new deficits showed CoMEP changes in only the muscle group or had preserved BR.

Although extremity MEP and SEP are noted to be not trustworthy in evaluating CNs, these modalities have an important place in the assessment of long tracts consisting of the corticospinal tract in MEP and the dorsal column-medial lemniscal path in SEP. In our practice, 16 patients had intraoperative SEP changes and 6 had MEP changes. However, only one patient had transient hemiparesis as new neurological deficit regarding extremities, which suggests that these modalities are powerful tools to determine the harm done to the long tracts.

Our policy is to stop the dissection at that surgical plane and allow neurological structures to recover. During this break, we let the IONM team to reevaluate SEP and MEP and interact with neuroanesthesia team to increase the blood pressure and correct other parameters.

These cumulative findings led us to form a policy regarding the surgical technique in posterior fossa surgeries assessed with IONM. According to this, surgical dissection was halted each time when surgeons were warned due to changes in IONM modalities. In the presence of amplitude decreaments of less than 50% or significant morphological changes, surgical dissection site has been changed to another part of the tumour, whether intracapsular or extracapsular. Further similar decreases or emergence of warning criteria led to the pause of the surgery until ameliorating signs in IONM were obtained. Such repeated periods in vestibuler schwannoma surgery may impose damage to facial nerve and cause deficit spesifically in presence of CoMEP warning signs and BR loss. On the other hand, our experience in epidermoids is a different case. Out of 9 epidermoids in this series, 3 had postoperative new facial palsy of HB 2. Warning criteria was detected in 2 and amplitude decreaments were seen in 1. At this step, we followed BR as a decision maker and continued surgery to achieve gross total resection in all the epidermoids.

However, significant acute decreases in facial CoMEP may hint damage to vascular supply of the facial nerve. In such cases, surgical team washes the surgical site around the nerve with warm saline and topical papaverine has been applied in some cases. Continuing the surgery in such cases during early times in this series always ended with disfiguring facial palsy.

## Conclusion

These findings show that neurophysiologic monitoring is an indispensable component of posterior fossa/skull base surgery. Multimodality monitoring rather than one modality provides a real-time, comprehensive assessment of nervous system function and allows for more aggressive management with safer surgical intervention and improved quality of life.

### Ethics

**Ethics Committee Approval:** The study was conducted with the approval of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethical Committee (ref no: 2020/70721) in concordance with the Declaration of Helsinki.

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

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## References

1. Macdonald DB. Intraoperative motor evoked potential monitoring: overview and update. J Clin Monit Comput 2006; 20: 347-77.
2. Toleikis JR, American Society of Neurophysiological Monitoring. Intraoperative monitoring using somatosensory evoked potentials. A position statement by the American Society of Neurophysiological Monitoring. J Clin Monit Comput 2005; 19: 241-58.
3. Rhoton AL Jr. Cerebellum and fourth ventricle. Neurosurgery 2000; 47: S7-27.
4. Deletis V, Urriza J, Ulkatan S, Fernandez-Conejero I, Lesser J, Misita D. The feasibility of recording blink reflexes under general anesthesia. Muscle Nerve 2009; 39: 642-6.
5. Neuloh G, Bogucki J, Schramm J. Intraoperative preservation of corticospinal function in the brainstem. J Neurol Neurosurg Psychiatry 2009; 80: 417-22.
6. Romstock J, Strauss C, Fahlbusch R. Continuous electromyography monitoring of motor cranial nerves during cerebellopontine angle surgery. J Neurosurg 2000; 93: 586-93.
7. Ulkatan S, Jaramillo AM, Tellez MJ, Goodman RR, Deletis V. Feasibility of eliciting the H reflex in the masseter muscle in patients under general anesthesia. Clin Neurophysiol 2017; 128: 123-7.
8. Dong CC, Macdonald DB, Akagami R, Westerberg B, Alkhani A, Kanaan I, et al. Intraoperative facial motor evoked potential monitoring with transcranial electrical stimulation during skull base surgery. Clin Neurophysiol 2005; 116: 588-96.
9. Deletis V, Fernandez-Conejero I, Ulkatan S, Costantino P. Methodology for intraoperatively eliciting motor evoked potentials in the vocal muscles by electrical stimulation of the corticobulbar tract. Clin Neurophysiol 2009; 120: 336-41.
10. Guideline 11A: Recommended Standards for Neurophysiologic Intraoperative Monitoring - Principles, in Society ACN (ed), 2009.
11. Morota N, Ihara S, Deletis V. Intraoperative neurophysiology for surgery in and around the brainstem: role of brainstem mapping and corticobulbar tract motor-evoked potential monitoring. Childs Nerv Syst 2010; 26: 513-21.
12. Simon MV, Michaelides C, Wang S, Chiappa KH, Eskandar EN. The effects of EEG suppression and anesthetics on stimulus thresholds in functional cortical motor mapping. Clin Neurophysiol 2010; 121: 784-92.
13. Polo G, Fischer C, Sindou MP, Marneffe V. Brainstem auditory evoked potential monitoring during microvascular decompression for hemifacial spasm: intraoperative brainstem auditory evoked potential changes and warning values to prevent hearing loss--prospective study in a consecutive series of 84 patients. Neurosurgery 2004; 54: 97-104.
14. Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JR. The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. Pediatr Neurosurg 1994; 20: 19-29.
15. Dubey A, Sung WS, Shaya M, Patwardhan R, Willis B, Smith D, et al. Complications of posterior cranial fossa surgery--an institutional experience of 500 patients. Surg Neurol 2009; 72: 369-75.
16. Fahlbusch R, Strauss C. [Surgical significance of cavernous hemangioma of the brain stem]. Zentralbl Neurochir 1991; 52: 25-32.
17. Deletis V, Fernandez-Conejero I, Ulkatan S, Rogic M, Carbo EL, Hiltzik D. Methodology for intra-operative recording of the corticobulbar motor evoked potentials from cricothyroid muscles. Clin Neurophysiol 2011; 122: 1883-9.
18. Prasad S, Hirsch BE, Kamerer DB, Durrant J, Sekhar LN. Facial nerve function following cerebellopontine angle surgery: prognostic value of intraoperative thresholds. Am J Otol 1993; 14: 330-3.
19. Deletis V, Fernandez-Conejero I. Intraoperative Monitoring and Mapping of the Functional Integrity of the Brainstem. J Clin Neurol 2016; 12: 262-73.

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# Intraoperative Cholangiography in Laparoscopic Cholecystectomy: Technique and Changing Indications

## Laparoskopik Kolesistektomide Peroperatuvar Kolanjiyografi: Teknik ve Değişen Endikasyonlar

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## ABSTRACT

**Introduction:** Although laparoscopic cholecystectomy (LC) is considered as the "gold standard" of cholecystectomy, the rate of bile duct injuries seems to be elevated when compared to open cholecystectomy. Intraoperative cholangiography (IOC) may prevent iatrogenic bile duct injuries or may diagnose missed bile duct injuries.

**Methods:** Between 1998 and 2016, 29 selective IOCs were performed in a total of 212 LCs (13.7%). At the beginning of the study (1998-2002), the indications of IOC were past history of jaundice, elevation of cholestatic enzymes and dilation of the common bile duct or suspicion of common bile duct stones on abdominal ultrasound, whereas obscure biliary anatomy became the main intraoperative criteria during the following years.

**Results:** Of the 29 patients, 20 were female and 9 patients were male. The mean age was 54.4 years. IOC was successful in 26 cases (90%). The median IOC time was 21.9 minutes. An anatomical variation was found in one patient. In this case, the cystic duct was opening into the right hepatic duct. The Wirsung duct was visualised in another patient, which was probably due to hyperpression of the sphincter of Oddi. No complication related to the procedure itself was encountered.

**Conclusion:** Although the routine use of IOC does not seem to be necessary, it may prevent bile duct injuries in selected cases. Surgeons should gain experience in performing the procedure, and the necessary equipment should be present in the operating room.

**Keywords:** Laparoscopic, cholecystectomy, intraoperative, cholangiography

## ÖZ

**Amaç:** Laparoskopik kolesistektomi (LK) günümüzde safra kesesi ameliyatlarında "altın standart" olarak kabul edilmiş olmakla birlikte, klasik kolesistektomi ile karşılaştırıldığında, iatrojenik safra yolu yaralanmalarında artışların meydana gelmiş olduğu görülmektedir. Laparoskopik peropratuvar kolanjiyografi (LPOK) uygulanması iatrojenik safra yolu yaralanmalarını önleyebilir ve gözden kaçmış olan bir yaralanmayı ortaya koyabilir.

**Yöntemler:** 1998-2016 yılları arasında LK yapılmış olan 212 olgudan 29 unda (%13,7) selektif LPOK uygulandı. LPOK uygulama endikasyonları çalışmanın başlangıcında (1998-2002), geçirilmiş sarılık, kolestaz enzimlerinde yükselme ve preoperatif ultrasonografide koledokta taş şüphesi veya dilatasyon saptanması iken, sonraki yıllarda endikasyonumuz peroperatuvar anatomik yapılardan emin olamama olarak değişti.

**Bulgular:** LPOK uygulanan olguların 20'si kadın, 9'u erkekti. Yaş ortalaması 54,4 idi. Toplam 26 (%90) hastada görüntülemede başarı sağlandı. Ortalama peroperatuvar kolanjiyografi süresi 21,9 dakika olarak ölçüldü. Bir hastada sistik kanalın sağ hepatik kanala açıldığı anatomik varyasyon görüntülendi. Bir hastada ise Wirsung kanalı görüntülendi ve bunun Oddi sfinkteri yüksek basıncına bağlı olduğu düşünüldü. Hiçbir hastada peroperatuvar kolanjiyografiye bağlı komplikasyon olmadı.

**Sonuç:** Genel kanı olarak, rutin LPOK kullanılması gerekli görülmemekle birlikte seçilmiş olgularda, iatrojenik safra yolu yaralanmalarını önleyebilir. Bu nedenle genel cerrahi uzmanlarının LPOK uygulanması konusunda tecrübe kazanmış olması ve gerekli altyapının ameliyathanede hazır bulunması gerekmektedir.

**Anahtar Kelimeler:** Laparoskopik, kolesistektomi, peroperatuar, kolanjiyografi

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## Introduction

The rate of iatrogenic bile duct injuries seems to be more elevated in laparoscopic cholecystectomy (LC) than in open cholecystectomy (1,2). The inflammatory process, adherence, intraoperative bleeding which may obscure good vision, common bile duct (CBD) tenting due to excessive traction, and anomalies of the biliary tract are all factors that are implicated in occurrence of iatrogenic bile duct injuries.

Biliary leakages or strictures may develop as a consequence of iatrogenic bile duct injuries necessitating several successive operations or endoscopic retrograde cholangiopancreatography (ERCP) procedures. Failure of these surgical or endoscopic procedures may give rise to increased morbidity and mortality rates (3,4). Bile duct injuries may lead to several medico-legal problems as well (1,3).

Routine or selective intraoperative cholangiography (IOC) may be an important tool to clearly delineate the biliary anatomy and to prevent an iatrogenic bile duct injury. On the other hand, IOC may diagnose a bile duct injury that has already occurred (3,4). The indications of IOC have been reduced recently, largely due to technical improvements concerning radiologic examinations such as abdominal ultrasound, computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP) and diagnostic or therapeutic ERCP.

In the present study, the medical reports of patients who underwent IOC were retrospectively examined in order to evaluate the necessity and utility of IOC.

## Methods

Ethical approval was waived in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. Written and oral consent was obtained from the patients included in the study, and their data were evaluated within the scope of the study. The medical records of 212 patients who underwent LC between 1998 and 2016 in SP hospital were retrospectively examined. Of these, 29 (13.7%) were submitted to IOC. The preoperative indications during the beginning period of the study (1998-2002) were history of jaundice, increase in cholestatsis enzymes and suspicion of CBD stones or dilation of CBD (>6 mm), whereas during the following years, the main indication became "obscure biliary tree anatomy" since preoperative radiologic examinations such as CT scan, MRCP and endoscopic procedures like ERCP eliminated other indications.

The age and gender of the patients, indications and the duration of IOC and results of cholangiograms were recorded. Patients were questioned regarding iodine allergy in preoperative period. Preoperative antibiotics were administered consisting of primary generation cephalosporins (Sefazol of 1 gr). The antibiotic course was not continued postoperatively.

### Technique of IOC

The patient was installed in a supine position. Both arms were in abduction of 80° while both legs were separated.The Surgeon was placed between the legs, and the assistant was situated on the left lateral side of the patient (French position).

LC was performed with four ports: The first port was umbilical with a diameter of 10 mm. The second port of 5 mm. diameter was introduced from the right lombar region on the anterior axillary line, between the anterior iliac spine and the point of the 12$^{th}$ rib. A third port of 5 mm. and a fouth one of 10 mm were placed in the subxyphoid and left hypochondrium respectively (Figure 1). A laparoscope of 30° angle was used.

The dissection of Calot's triangle and identification of the cystic duct and cystic artery was followed by the application of a titanium clip proximally on the cystic duct, close to the infundibulum. Care was taken to keep a distance of at least 1.5 cm from the common bile duct. A small hemicirconferential incision was made just distal to the clip. A 15-gauge, 12-cm long "Cystic Duct Access Trocar Sheath Needle" (COOK Medical Inc. Bloomington, IL, USA) was introduced from the midline, on the line rejoining port no: 2 and no: 4, on the midclavicular line (no: 5- Figure 1). A 4F or 6F urinary catheter was inserted into the peritoneal cavity via the needle depending on the thickness of the cystic duct. The infundibulum of the gallbladder was grasped, and right inferolateral traction was applied by grasper forceps introduced through port no: 2. The catheter was grasped leaving a 2 cm free margin from its distal tip by another grasping forceps inserted through port no: 3. The cystic duct was catheterized and loosely regrasped.

The permeability of the catheter was varified by flushing 2 or 3 mL of saline solution into the lumen. After making sure that it was water tight, the abdominal cavity was deflated.

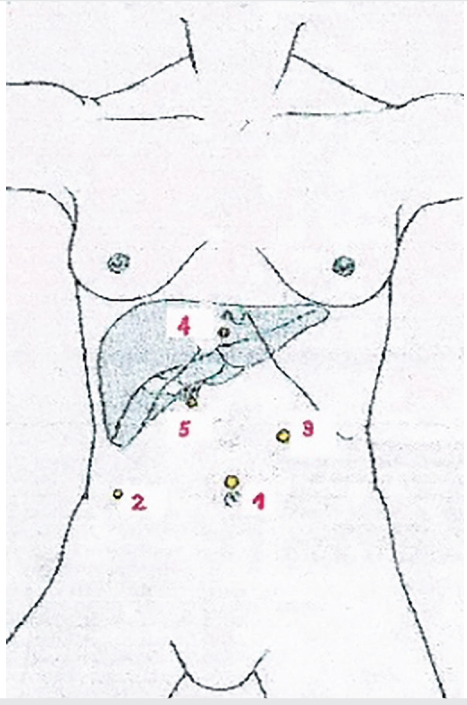


**Figure 1.** The location of ports

1. Umbilical (10 mm)
2. Right lombar (on anterior axillary line, between anterior iliac spine and the point of the 12$^{th}$ rib) (5 mm)
3. Left hypochondrium 10 mm
4. Subxyphoid on middle line (5 mm)
5. Puncture site for introduction of cholangiography catheter

A C-arm radiological unit was focused on the right hypochondrium. 10 mL of contrast dye (10 mL of 1/3 diluated Urografin) was administered into the catheter until the common bile duct was completely visualized. The passage of the contrast media into the duodenum was verified, and dynamic images were obtained. In order to visualize the proximal and intrahepatic bile ducts, an additional amount of contrast media of 10 mL was injected via the catheter, and the patient was placed in Trendelenburg position.

Consequently, cholangiogram images were printed (Figure 2).

Common bile duct and intrahepatic bile duct anatomy and diameter, the presence of lacunar calcula image, the passage of contrast media into the duodenum, the visibility of Wirsung duct and the presence of contrast media leakage were evaluated. The maneuver time was measured as the duration between the passing and the extraction of the catheter from the peritoneal cavity.

Peritoneal cavity was reinsufflated, and the catheter was extracted. Two additional titanium clips were placed distal to the cystic duct incision and the duct was sectioned.

The section of the cystic artery was performed after the IOC procedure in all cases.

### Statistical Analysis

As statistical evaluation of continuous variables arithmetic mean ± standard deviation and minimum-maximum values and for the discrete (qualitative) variables % share ratios were presented as descriptive statistics.

## Results

IOC was performed in 29 (13.7%) out of 212 patients who underwent LC. Twenty patients were female, 9 patients were male. The mean age was 54.4±3.8 years (minimum-maximum: 27-83). IOC was successful in 26 (90%) patients in which the biliary anatomy was perfectly deliniated. In 3 patients, IOC was not possible due to impossible catheterization of the cystic duct.

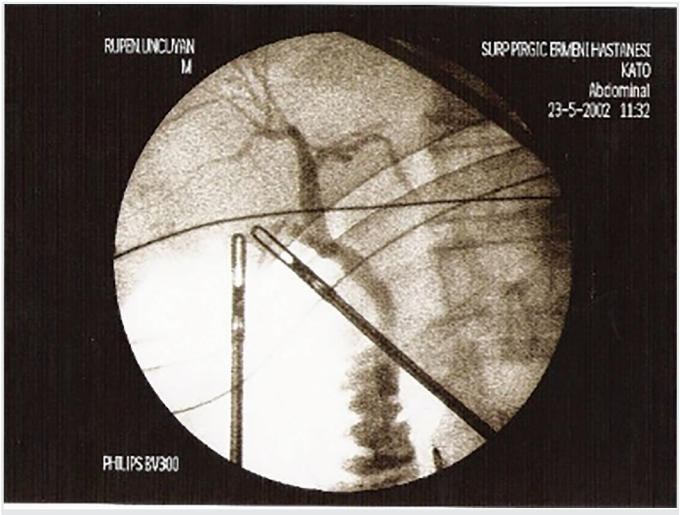


**Figure 2.** The position of instruments during IOC
1. Left grasper on Hartmann's pouch (port number 2)
2. Right grasper on distal end of cystic duct (port number 3)
IOC: Intraoperative cholangiography

The indications of IOC are presented in Table 1.

The median exploration time was 21.9±4.3 minutes with a variable range between 15 and 40 minutes mostly due to cholangiogram interpretation.

In 26 patients where IOC was successful, the distance between the proximal clip and bile duct was greater than 1 cm., the passage of contrast media into the duodenum was normal, and the bile duct anatomy was clearly identified. No lacunary images and no leakage of contrast media from the bile ducts was present.

In one patient, an anatomic variation was found where the cystic duct was opening into the right hepatic duct. In another patient, the Wirsung duct was visualized due to hyperpression of the sphincter of Oddi.

Symptomatic gall bladder stones were present in three unsuccessful cases.

No IOC related complications were observed. All patients except one were discharged the day after the operation.

In one patient, an increase in levels of direct bilirubin and cholestatic enzymes was observed. The IOC was considered normal in this patient. The elevated levels persisted until 5$^{th}$ postoperative day. The patient was discharged on the 6$^{th}$ day without any additional radiologic examinations. The follow-up examinations performed one month later showed no laboratory or radiologic abnormalities. No problem was encountered 3 years after the operation. No IOC was performed for intraoperative suspicion of bile duct injury.

## Discussion

In the modern surgical era, the majority of cholecystectomies are performed laparoscopically, which is considered as "gold standard" of cholecystectomy. LC has several advantages such as improved cosmesis, reduced period of hospital stay and rapid convalescence, and no incidence of postoperative incisional hernias due to Kehr incision. The incidence of common bile duct injuries following LC, when compared to open cholecystectomy, has been shown to be more elevated as a side effect of this trend. Some studies have reported rates of iatrogenic bile duct injury between 0.2 to 1.1% (1,2,5).

The adherences and fibrosis which may be formed as a consequence of repeated cholecystitis attacks, past surgical operations, intraoperative

**Table 1. Indications of intraoperative cholangiography**

| Indication | Number of patients |
|---|---|
| Increase in cholestasis enzymes | 10 |
| History of jaundice | 3 |
| Suspicion of common bile duct stones and preoperative ERCP | 2 |
| Dilation of common bile duct (>6 mm) | 5 |
| Obscure biliary tree anatomy | 9 |

ERCP: Endoscopic retrograde cholangiopancreatography

bleeding which may obscure good vision, the tenting of common bile duct due to excessive traction, the experience of the surgeon are all factors that are accused in occurance of iatrogenic bile duct injuries (5,6).

Bile duct injuries, whether diagnosed intraoperatively or postoperatively, are subject to several difficulties while exposing the patient to several invasive explorations such as repeated radiologic examinations, surgical interventions or endoscopic procedures like ERCP. ERCP is quite efficient in the management of ductal stones, and it has a morbidity rate of 7-11% and a mortality of <1%, especially if accompanied by endoscopic sphincterotomy (7). As a consequence, the life quality of the patient is lowered and morbidity and mortality rates are increased (4,6).

IOC represents an important tool in diagnosing unsuspected CBD stones during LC performed either routinely or selectively. IOC may also deliniate the anatomy of the biliary tree, may prevent serious intraoperative complications and may decrease the morbidity and mortality rates (8).

At the beginning of laparoscopic experience, some authors have advocated routine use of IOC, which can detect significantly more biliary injuries as well as unexpected biliary anatomy of potential surgical relevance despite an increase in operative time and cost (9-13). On the other hand, false positive results may lead to unnecessary Common Bile Duct explorations or ERCP (11).

Stewart and Way (14) identified the two most important reasons for ductal injury during LC as: (a) false identification of CBD as the cystic duct and (b) aggressive efforts to stop bleeding. They outlined liberal use of IOC and cautious interpretation of the lack of opacification of the proximal CBD as a sign of its closure.

Wright and Wellwood (15) concluded that meticulous dissection of calots triangle is a more reliable safeguard against bile duct injuries than routine IOC. If the ductal anatomy is unclear, IOC or open conversion should be performed.

Collins et al. (16) concluded that treatment decision based on assessment by IOC alone would result in unnecessary intervention in 50% of patients who had either false positive studies or subsequently passed the stone, and one third of the patients with CBD stone at the time of cholecystectomy pass their stones spontaneously within 6 weeks of surgery.

Actually, many authors reserve IOC to selective cases when the biliary anatomy is not clearly defined intraoperatively or when iatrogenic bile duct injury is suspected. Variation in the biliary anatomy is common, and the incidence reported in the literature is around 10 to 28% (17,18). This has often been cited as a justification for the routine use of IOC to reduce the incidence of bile duct injury (19-21). However, review of the literature does not show any association between the occurance of anomalous anatomy and bile duct injuries (22).

Although the improvement of preoperative diagnostic tools has led to a decrease in indications of IOC, it still has to be performed in selected cases in patients with high and intermediate risk of CBD stones who have not had a preoperative MRCP if ductal anatomy is unclear during LC (6,8).

In another study, methylene blue was injected in the gallbladder in order to visualize the anatomy of the biliary tree. It was stated that a decreased rate of iatrogenic bile duct injury was obtained by this technique. The leakage of methylene blue was easily demonstrated, and the staining of the duodenum indiretly proved the presence of intact common bile duct (23).

The success rates are given between 60 to 90%, and unsuccessful procedures are mostly due to the presence of very thin cystic ducts (8,24). Our results, with a success rate of 90%, are in correlation with these studies.

We performed IOC with wider indications at the beginning of our experience, but during the following years, the indications were mostly limited to intraoperative suspicion of obscure biliary anatomy. We think that this was largely due to technical improvement of radiologic examinations such as CT scan, MRCP and endoscopic examinations like ERCP.

The average IOC time is given as 20 minutes which is in accordance with our results (25). We found an average IOC time as 21.9 minutes. The average time for performing IOC was progressively shortened, while the experience was accumulated. Despite the limited number of cases included in the present study, we may conclude that especially at the beginning of the experience concerning LC, an average additional time of 21.9 minutes facilitated the identification of cystic duct and common bile duct and a bile duct injury was possibly prevented. In one case where the cystic duct was opening to the right hepatic duct, the performance of IOC avoided an injury to the right hepatic duct.

No additional intraoperative technical difficulty was encountered in patients who presented with acute cholecystitis in patients with a history of acute edematous pancreatitis or in patients who underwent preoperative ERCP procedure. No intraoperative or postoperative complications were encountered due to the procedure itself.

## Conclusion

In current practice, although the routine use of IOC is not recommended, it is crucial for every surgeon performing LC to be able to perform the IOC technique and to interpret the dynamic cholangiography and/or cholangiograms. The necessary radiologic equipmemt (C-arm X-ray device) should always be available in the OR.

### Ethics

**Ethics Committee Approval:** Ethical approval was waived in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

**Informed Consent:** Written and oral consent was obtained from the patients

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

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

## References

1. Dolan JP, Diggs BS, Sheppard BC, Hunter JG. Ten-year trend in the national volume of bile duct injuries requiring operative repair. Surg Endosc 2005; 19: 967-73.

2. Waage A, Nilsson M. Iatrogenic bile duct injury: a population-based study of 152 776 cholecystectomies in the Swedish Inpatient Registry. Arch Surg 2006; 141: 1207-13.

3. Kapoor VK. Medico-legal aspects of bile duct injury. J Minim Access Surg 2016; 12: 1-3.

4. Törnqvist B, Strömberg C, Akre O, Enochsson L, Nilsson M. Selective intraoperative cholangiography and risk of bile duct injury during cholecystectomy. Br J Surg 2015; 102: 952-8.

5. Melton GB, Lillemoe KD, Cameron JL, Sauter PA, Coleman J, Yeo CJ. Major bile duct injuriesassociated with laparoscopic cholecystectomy: effect of surgical repair on quality of life. Ann Surg 2002; 255: 888-95.

6. Jenny MLR, Agneta KM. Quality-of-life after bile duct injury: intraoperative detection is crucial. A national case-control study. HPB (Oxford) 2016; 18: 1010-6.

7. Phillips EH. Routine versus selective intraoperative cholangiography. Am J Surg 1993; 165: 505-7.

8. Philips EH, Berci G, Carroll B, Daykhovsky L, Sackier J, Paz-Partlow M. The Importance of Intraoperative cholangiography during laparoscopic cholecystectomy. Am Surg 1990; 56: 792-5.

9. Photi ES, El-Hadi A, Brown S, Swafe L, Ashford-Wilson S, Barwell J, et al. The Routine Use of Cholangiography for Laparoscopic Cholecystectomy in the Modern Era. JSLS 2017; 21: e2017.00032.

10. Flowers JL, Zucker KA, Graham SM, Scovill WA, Imbembo AL, Bailey RW. Laparoscopic cholangiography. Results and indications. Ann Surg 1992; 215: 209-16.

11. Borjeson J, Liu SK, Jones S, Matolo NM. Selective intraoperative cholangiography during laparoscopic cholecystectomy: how selective? Am Surg 2000; 66: 616-815.

12. Flum DR, Dellinger EP, Cheadle A, Chan L, Koepsell T. Intraoperative cholangiography and risk of common bile duct injury during cholecystectomy. JAMA 2003; 289: 1639-44.

13. Fletcher DR, Hobbs MS, Tan P, Valinsky LJ, Hockey RL, Pikora TJ, et al. Complications of cholecystectomy: risks of the laparoscopic approach and protective effects of operative cholangiography: a population based study. Ann Surg 1999; 229: 449-57.

14. Stewart L, Way LW. Bile duct injuries during laparoscopic cholecystectomy. Factors that influence the results of treatment. Arch Surg 1995; 130: 1123-8.

15. Wright KD, Wellwood JM. Bile duct injury during laparoscopic cholecystectomy without operative cholangiogram. Br J Surg 1998; 85: 191-4.

16. Collins C, Maguire D, Ireland A, Fitzgerald E, O'Sullivan GC. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited. Ann Surg 2004; 239: 28-33.

17. Goor DA, Ebert PA. Anomalies of the biliary tree. Arch Surg 1972; 104: 302-9.

18. Hamlin JA. Biliary duct anomalies. In: Berci G, Hamlin JA, editors. Operative biliary radiology. Baltimore: Williams & Wilkins; 1981.p.109-35.

19. Walters W, Philips SK. The increasing frequency of injury of the common bile duct, hepatic duct. Surgery 1949; 25: 469-75.

20. Foster JH, Wayson EE. Surgical significance of aberrant bile ducts. Am J Surg 1962; 104: 14-20.

21. Moosman DA, Coller FA. Prevention of traumatic injury to the bile ducts. Am J Surg 1951; 82: 132-7.

22. Metcalfe MS, Ong Thao, Bruening Martin H, Iswariah Harish, Wemyss Holden Simon A, Maddern Guy J. Is laparoscopic intraoperative cholangiogram a matter of routine? Am J Surg 2004; 187: 475-81.

23. Sarı YS, Tunalı V, Tomaoglu K, Karagöz B, Güney A, Karagöz. Can bile duct injuries be prevented? "A new technique in laparoscopic cholecystectomy". BMC Surg 2005; 5: 14.

24. Berci G, Sackier J, Paz-Partlow M. Routine or selective intraoperative cholangiography during laparoscopic cholecystectomy. Am J Surg 1991: 161: 355-60.

25. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: The Dundee technique. Br J Surg 1991; 78: 155-9.

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# Significantly Lower Serum Adiponectin Levels in the Postmenopausal Age may be Specific for Breast Cancer Risk

## Postmenopozal Meme Kanserinde Anlamlı Düşük Serum Adiponektin Düzeyleri

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## ABSTRACT

**Introduction:** To date, biomarkers have played a minimal role in the early diagnosis of breast cancer. Although its effects on metabolism are not well known, studies have shown that hypoadiponectinaemia is associated with increased insulin resistance and risk for type-2 diabetes. We aimed to investigate the value of adiponectin together with laboratory results, anthropometric measurements and histopathological findings in assessing the risk of breast cancer and for use in early diagnosis.

**Methods:** In this study, serum samples were obtained from 59 recently diagnosed breast cancer patients and 47 cancer-free controls aged between 22 and 82 years to assay serum adiponectin, lipids, fasting blood glucose and insulin; homeostatic model assessment for insulin resistance (HOMA-IR) and body mass index were calculated using the anthropometric measurements. Histopathologic findings were extracted from the patients' files.

**Results:** Our results revealed that adiponectin serum levels and HOMA-IR values were significantly different between patients and controls. In addition, serum adiponectin levels were lower in postmenopausal breast cancer patients compared to the controls (p=0.03).

**Conclusion:** In fact, a serum adiponectin level below 4.46 mg/L may be in favour of postmenopausal breast cancer (area under the curve =70%). However, Cerb-B2 expression in patients did not correlate with serum adiponectin levels. These findings have implications for further research on adiponectin as well as the in early diagnosis of postmenopausal breast cancer with possibly higher test sensitivity.

**Keywords:** Adiponectin, insulin resistance, early diagnosis of breast cancer, body mass index, serum lipids

## ÖZ

**Amaç:** Meme kanseri erken tanısında, serum biyomarker düzeyleri kullanımı sınırlı kalmaktadır. Metabolizması tam olarak bilinmese de, hipoadiponektinemi ile artmış insülin direnci ve tip II diyabet riski arasında ilişkili olduğu gösterilmiştir. Bu çalışmada, serum adiponektin düzeylerinin antropometrik ölçümler ve diğer laboratuvar bulgularıyla birlikte meme kanseri tanısındaki klinik yararını araştırmayı amaçladık.

**Yöntemler:** Çalışmamızda 22-82 yaş arası kadınlarda meme kanseri hastası (N=59) ve kontrol grubunu oluşturan sağlıklı bireylerden (N=47) alınan kan örneklerinde adiponektin, lipidler, açlık kan şekeri ve insülin düzeyleri ölçüldü ve insülin direnci için homeostatik model değerlendirmesi (HOMA-IR), vücut kitle indeksi hesaplandı. Histopatolojik veriler hasta dosyalarından elde edildi. Anamnez, folikül uyarıcı hormon ve luteinleştirici hormon düzeylerine göre hastalar premenapoz ve postmenapoz olarak sınıflandırıldı.

**Bulgular:** Sonuçlarda, meme kanseri hastalarının adiponektin ve HOMA-IR düzeyleri ile kontrol grubununkiler arasında anlamlı fark görülmüştür. Ayrıca postmenopozal hastaların serum adiponektin düzeyleri kontrollere göre anlamlı düşük bulunmuştur (p=0,03).

**Sonuç:** Aynı zamanda, 4,46 mg/L altındaki serum adiponektin düzeyleri, postmenopozal meme kanserine spesifite göstermektedir (eğri altındaki alan =%70). Ancak, Cerb-B2 ekspresyonu adiponektin ile korele bulunmamıştır. Bu sonuçlara göre, daha çok örnekle özellikle postmenopozal grupta yapılacak çalışmalar, adiponektinin erken tanıda daha yüksek hassasiyete sahip olduğunu ortaya çıkarabilir ve bu amaçla kullanılmasını destekleyecek sonuçlar verebilir.

**Anahtar Kelimeler:** Adiponektin, insülin direnci, meme kanserinde erken tanı, vücut kitle indeksi, lipidler

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## Introduction

Breast cancer is the most common type of cancer among women. It is estimated that over 627,000 women died of breast cancer in 2018 worldwide (1). Also, the incidence rates vary greatly worldwide (2).

Danaei et al. (3) calculated the contribution of modifiable risk factors for breast cancer and concluded that 21% of all breast cancer deaths are attributable to obesity/overweight and physical inactivity together with alcohol use.

Adiponectin, a 30kD peptide discovered in 1995 by Scherer et al. (4), is secreted in adipose tissue. It is found in lower levels in patients diagnosed with obesity-associated cancers and its synthesis is inhibited in obese subjects. Plasma adiponectin concentrations are inversely correlated with body mass index (BMI) (5). Adiponectin has insulin-sensitising, anti-inflammatory, anti-atherogenic, anti-neoplastic and cardioprotective effects (6). It has been shown to inhibit the proliferation of several cancer-derived cells including breast, endometrium, prostate and colorectal cancer. Surprisingly, it exhibits both pro and anti-angiogenic characteristics. Adiponectin acts indirectly by modulating insulin sensitivity in the breast epithelium, influencing tumour angiogenesis and regulating the inflammatory responses (6).

Hypoadiponectinaemia, which is the result of both genetic and/or environmental factors, is associated with several disorders like insulin resistance, diabetes mellitus type-2, hypertension and several malignancies (7). Specifically, low adiponectin levels promote fatty acid and protein synthesis, as well as cell growth and proliferation (8).

Most studies showed significantly low adiponectin levels in breast cancer patients compared to healthy controls. While some of these studies found no relationship at all, others found even higher adiponectin levels in patients compared to controls. On the other hand, a study by Karaduman et al. (9), showed significantly higher levels of adiponectin in breast tumour tissue compared to the control group. There is evidence that a higher ratio of leptin, another adipokin, to adiponectin may be a sign of the presence of aggressive breast cancers (10).

The objective of this study was to assess serum levels of adiponectin in breast cancer patients and healthy controls with respect to the menopausal status and indicators of obesity, BMI and interventional radiology. We also aimed to investigate the relationship between serum adiponectin levels and histopathological tissue Cerb-B2 receptor status.

## Methods

This study was conducted in compliance with the Good Clinical Practice guidelines and the ethical principles stated in the Declaration of Helsinki, and was approved by the Ethical Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital under report numbered 469. Sixty-eight women with signs of breast cancer who had been treated in the Surgery Department of University of Health Sciences Turkey, İstanbul Training and Research Hospital between February 2012 and February 2013 were enrolled into our study. All the patients gave written consent to participate in the study. Nine of them were excluded either because they were misdiagnosed or laboratory results were inconsistent. Breast cancer diagnosis was based on biopsy results. Serum samples after 8 hours of fasting had been obtained from the patients during their stay in the hospital. Demographic data of the patients were obtained from the patients' file. Weight, height and waist circumference were measured at the time of blood withdrawal. Blood tests ordered by the physician were ran and serum samples were later stored at -80°C.

Forty-seven healthy women, without known breast cancer confirmed by mammo-ultrasonography, comprised our control group. Serum samples were collected in the ambulatory clinic and later frozen until analysis.

Exclusion criteria for the patient group were as follows:

1. Patients already diagnosed with malignant disease other than breast cancer
2. Patients who received any form of cancer therapy (surgery, radiotherapy, chemotherapy)
3. Biopsy result rejected the diagnosis of breast cancer

A total of 59 patient and 47 control samples were defrosted and in turn ran using the Human Adiponectin ELISA (Hangzhou Eastbiopharm Co. Ltd.) on June the same year (Cat. No: CK-E10871). Reference ranges for women were defined as 2-30 mg/L, with an analytical range of 0.2-60 mg/L and LoD of 0.11 mg/L. Insulin levels were measured by the ECLIA method using DXI 800 (Beckman-Coulter Inc., USA). Fasting serum glucose (FSG), total cholesterol, triglyceride, high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C) levels were measured by photometric method using commercial reagents on AU 2700 (Beckman-Coulter Inc., USA). Menopausal statuses of the patients were determined by combining the data of age at diagnosis, FSH and luteinizing hormone measurements or menstruation history in the patient records.

Insulin resistance was calculated as homeostatic model assessment for insulin Resistance (HOMA-IR) using formula:

$$\text{HOMA-IR} = \frac{\text{Glucose (mg/dL)} \times \text{Insulin (mU/L)}}{405}$$

BMI was calculated based on the following formula: bodyweight in kilograms divided by height in metres squared.

CerbB2 immunostaining pattern was noted as a score of 0, 1, 2 and 3; cases with score 0 and 1 were accepted as negative for overexpression. Cases with score 3 alone and score 2, but with verified positivity for overexpression by an *in situ* hybridisation method were accepted as positive.

### Statistical Analysis

Statistical data was analysed using SPSS 15.0 for Windows. For comparing two independent groups, Student t-test was used for normally distributed variables and Mann-Whitney U for non-Gaussian distributed variables. For comparing more than two independent groups, One-Way ANOVA test was used for normally distributed variables and Kruskal-Wallis test for non-Gaussian variables. Sub-group analyses were performed using Tukey's test for parametric and Mann-Whitney U test

for non-parametric tests and Bonferroni correction was implemented. The Spearman Correlation method was used for non-parametric tests. Factors that increase the risk for breast cancer were evaluated using Logistic Regression Forward method. For all comparisons, a level of $p<0.05$ was considered statistically significant.

## Results

Demographic and laboratory data were compared in Table 1. Adiponectin but not HOMA-IR was found to be significantly lower in the patient group compared to the control group (p=0.020; Table 1, Figures 1,2). Neither HOMA-IR nor adiponectin proved to be correlated with any of the parameters shown on Table 2 in the patient and control groups (p=0.061, p=0.468). HOMA-IR was positively correlated with FSG, insulin and BMI in the patient group and age, FSG, insulin, triglyceride and BMI in the control group (Table 2).

Adiponectin was significantly lower in the premenopausal group compared to the postmenopausal group (p=0.015). We evaluated the groups with respect to the menopausal status, comparing adiponectin and BMI values. In the patient group, BMI was significantly higher in the postmenopausal group compared to the premenopausal group (p=0.008; Figure 3, Table 3).

**Table 1. Demographic information and biochemical parameters of the patient and control groups**

| | Patients (n=59) | Controls (n=47) | |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | p |
| Age (year) | 52.49±13.81 | 49.91±9.76 | 0.267 |
| BMI (kg/m$^2$) | 27.92±5.45 | 28.46±4.45 | 0.277 |
| FSG (mg/dL) | 110.81±43.42 | 94.0±8.98 | 0.096 |
| Insulin(mU/L) | 7.02±5.11 | 9.21±5.27 | 0.008 |
| Total cholesterol (mg/dL) | 209.75±43.77 | 220.91±47.84 | 0.214 |
| Triglyceride (mg/dL) | 131.36±74.75 | 120.49±50.75 | 0.834 |
| HDL-C (mg/dL) | 53.32±15.76 | 59.84±14.88 | 0.023 |
| LDL-C (mg/dL) | 131.64±40.72 | 136.89±39.82 | 0.288 |
| Adiponectin (mg/L) | 5.18±2.61 | 6.45±3.94 | 0.020 |
| HOMA-IR | 1.99±1.72 | 2.17±1.32 | 0.131 |

FSG: Fasting serum glucose, BMI: body mass index, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, HOMA-IR: homeostatic model assessment for insulin resistance, SD: standard deviation

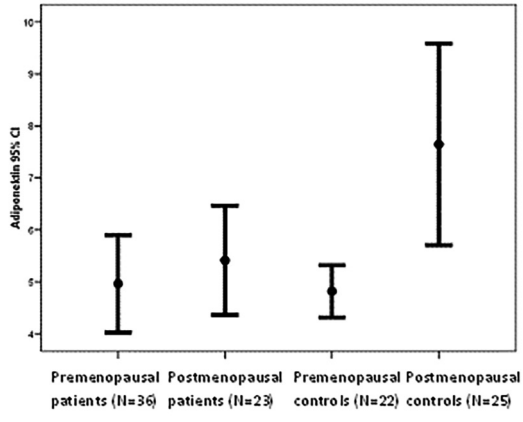


**Figure 1.** Plot graph showing distribution of serum adiponectin levels through sub-groups according to menapausal status, $N_{patients}=59$; $N_{controls}=47$

CI: Confidence interval

## Discussion

Current research on breast cancer, mainly focuses on early diagnosis, treatment and detection of relapses. Early diagnosis in breast cancer is life-saving and significant for public health.

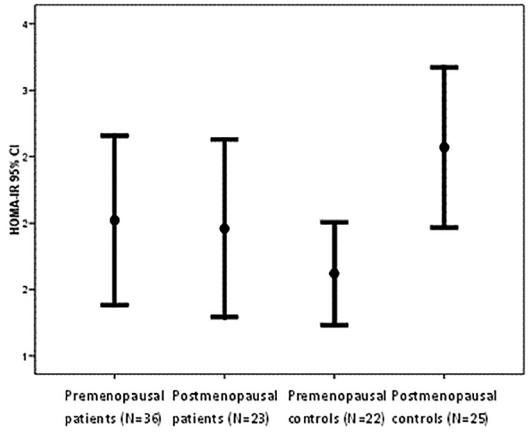


**Figure 2.** Plot graph showing distribution of HOMA-IR values $N_{patients}=59$; $N_{controls}=47$

HOMA-IR: Homeostatic model assessment for insulin resistance, CI: confidence interval

**Table 2. Correlation of studied parameters with adiponectin and HOMA-IR values in the patient and control groups**

| | | Adiponectin | | HOMA-IR | |
|---|---|---|---|---|---|
| | | r | p | r | p |
| Patients (n=59) | HOMA-IR | 0.245 | 0.061 | - | - |
| | Age (year) | 0.139 | 0.292 | 0.085 | 0.523 |
| | FSG (mg/dL) | 0.206 | 0.117 | 0.497 | <0.001 |
| | Insulin (mU/L) | 0.227 | 0.084 | 0.945 | <0.001 |
| | T. cholesterol (mg/dL) | -0.020 | 0.883 | -0.023 | 0.865 |
| | Triglyceride (mg/dL) | 0.097 | 0.465 | 0.116 | 0.381 |
| | HDL-C (mg/dL) | 0.020 | 0.883 | -0.004 | 0.973 |
| | LDL-C (mg/dL) | -0.021 | 0.877 | -0.049 | 0.712 |
| | BMI (kg/m$^2$) | 0.075 | 0.573 | 0.265 | 0.043 |
| Control (n=47) | HOMA-IR | -0.111 | 0.468 | - | - |
| | Age (year) | 0.163 | 0.284 | 0.329 | 0.027 |
| | FSG (mg/dL) | 0.073 | 0.635 | 0.411 | 0.005 |
| | Insulin (mU/L) | -0.147 | 0.334 | 0.977 | <0.001 |
| | T. cholesterol (mg/dL) | 0.166 | 0.275 | 0.061 | 0.690 |
| | Triglyceride (mg/dL) | 0.031 | 0.839 | 0.441 | 0.002 |
| | HDL-C (mg/dL) | 0.046 | 0.765 | -0.175 | 0.249 |
| | LDL-C (mg/dL) | 0.252 | 0.095 | -0.101 | 0.509 |
| | BMI (kg/m$^2$) | 0.046 | 0.764 | 0.470 | 0.001 |

T.cholesterol: Total cholesterol, FSG: fasting serum glucose, BMI: body mass index, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, HOMA-IR: homeostatic model assessment for insulin resistance

Adiponectin but not HOMA-IR was found to be lower in the patients compared to controls (p=0.020; Table 1). This finding has actually been proven in several studies up-to-today (11-13), and was a result that we expected.

Previous studies have shown that BMI values are associated with postmenopausal breast cancer risk. In fact, Ahn et al. (14) hypothesised that weight gain during the adult life is associated with increased risk for postmenopausal breast cancer. More recent studies have also shown a significant increase in breast cancer risk after weight gain (15), especially in postmenopausal women (16,17). In our study; however, we found no significantly high BMI values in the postmenopausal patients compared to controls (p=0.822; Table 3).

Triglyceride levels in the controls seem to be correlated with HOMA-IR; however, in the patient group they were discordant. HOMA-IR was well correlated with BMI in both groups (Tables 2, 4).

There was a prominent difference in BMI values between the pre- and postmenopausal groups, which may result from the significant difference in age between these groups (Table 3).

Studies show some disorders associated with adiponectin such as obesity and insulin resistance (13,18,19). BMI, used widely as a measure of obesity, is well documented (6,13). Low levels of serum adiponectin and increased insulin resistance together with increased BMI have already been shown in breast cancer patients in some studies (13,20,21). However, none of the parameters investigated in our study including BMI and HOMA-IR was found to be correlated with adiponectin (Table 4).

Körner et al. (12) have also concluded that adiponectin levels in breast cancer patients were lower irrespective of age, BMI, parity, insulin or family history. When we specifically consider the postmenopausal group, adiponectin levels were lower in the patients. In fact, in this group, we found that lower serum adiponectin and higher age are risk factors for postmenopausal breast cancer (Table 5).

Another surprising result in the postmenopausal group was that HOMA-IR values were significantly lower in the patients (p=0.016; Table 5).

In a review of a prospective study conducted by Endogenous Hormones and Breast cancer Collaborative Group (Key et al.) (22), relative risk (RR) for breast cancer was calculated in postmenopausal women with respect

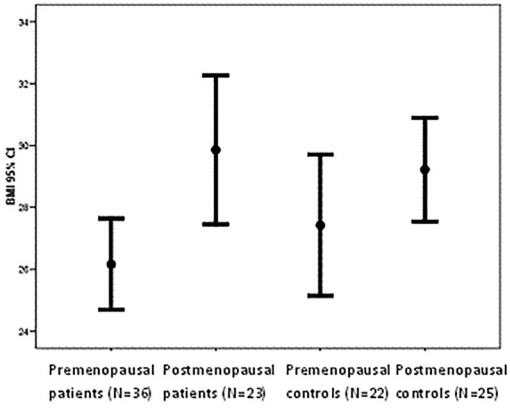


**Figure 3.** Plot graph of BMI values, Npatients=59; Ncontrols=47

BMI: Body mass index, CI: confidence interval

**Table 3. Comparing p values of adiponectin and body mass index values with respect to the sub-groups**

| | Premenopausal (n=52) | Postmenopausal (n=54) | |
|---|---|---|---|
| **Adiponectin (mg/L)** | 4.91±2.09 | 6.49±3.99 | 0.015 |
| | | | |
| | | **Adiponectin** | **BMI** |
| | | **p** | **p** |
| **Premenopausal patient** | Postmenopausal patient | 0.642 | 0.008 |
| | Premenopausal control | 0.830 | 0.358 |
| | Postmenopausal control | 0.006 | 0.015 |
| **Postmenopausal patient** | Premenopausal control | 0.997 | 0.329 |
| | Postmenopausal control | 0.143 | 0.822 |
| **Premenopausal control** | Postmenopausal control | 0.147 | 0.115 |

BMI: Body mass index

**Table 4. Correlation of adiponectin with body mass index in the postmenopausal group**

| **Correlations** | | | | | |
|---|---|---|---|---|---|
| | | | **BMI** | **IR** | **Adiponectin** |
| **Spearman's rho** | **BMI** | Correlation coefficient | 1.000 | 0.421** | 0.010 |
| | | Sig. (2-tailed) | - | 0.003 | 0.945 |
| | | N | 48 | 48 | 48 |
| | **IR** | Correlation coefficient | 0.421** | 1.000 | 0.037 |
| | | Sig. (2-tailed) | 0.003 | - | 0.804 |
| | | N | 48 | 48 | 48 |
| | **Adiponectin** | Correlation coefficient | 0.010 | 0.037 | 1.000 |
| | | Sig. (2-tailed) | 0.945 | 0.804 | - |
| | | N | 48 | 48 | 48 |

**: Correlation is significant at the 0.01 level (2-tailed), BMI: body mass index, IR: interventional radiology, Sig.: significance

to BMI tertiles. In addition to oestradiol, some other steroid hormones and sex hormone binding globulin (SHBG) have also been assayed (23). Calculating RR adjusting for the results of these tests yielded less significant increased risk in the high-BMI group. This raises the idea that oestrogens might play a major role in postmenopausal breast cancer risk rather than obesity.

To investigate the difference in adiponectin serum levels between patients and controls, we set three intervals for adiponectin concentration to see if there was a significant trend toward patients in the low adiponectin group. However, this did not yield a significant difference between the groups (Table 6; $p<0.325$).

Histopathologic Cerb-B2 expression in breast cancer patients was not associated with serum adiponectin-to-BMI ratio. Cubukcu et al. (24) found no associations between adiponectin histochemical expression and prognosis. Karaduman et al. (9) also conducted similar research with tissue adiponectin levels to find similar results in Turkish population. Our results are one of the very few of its kind in a Turkish population (Table 7).

For the postmenopausal group, the difference in adiponectin levels between patients and controls was more significant. Therefore, we calculated the area under the curve (AUC) for breast cancer risk and adiponectin levels; a concentration below 4.46 mg/L had 70% AUC, 80% specificity and 52% sensitivity for breast cancer. We wanted this test to have a high sensitivity at maximum AUC. However, it was quite low. This is only a preliminary model and we believe that this study could provide more reliable outcome for clinical use if it will be repeated with higher number of samples (Figure 4).

A review on use of adiponectin as a routine clinical biomarker, suggests that hypoadiponectinemia, a serum level of <4 mg/L, is associated with several diseases including postmenopausal breast cancer, although not specifically (19). A recent meta-analysis concludes that pre and postmenopausal breast cancer patients have significantly lower serum adiponectin levels compared to controls and that adiponectin may serve as a biomarker of breast cancer risk and help to identify subjects at high risk for breast cancer development (25).

We found no significant difference in triglyceride levels between the patient and control groups, which is in line with the results of a recent meta-analysis (26). A cohort study of 3537 cases showed relatively lower HDL-C, LDL-C and total cholesterol levels in breast cancer patients with age stratification. LDL-C and total cholesterol levels were still lower in the patient group compared to the controls (27). In our study, HDL-C levels were lower in the patient group compared to the controls. However LDL-C levels did not show a significant difference.

A drawback of our study was that it lacked serum levels of oestradiol, SHBG and other steroid hormones. For this reason, it is challenging to tell if the increase in breast cancer risk associated with increasing BMI values was a result of the oestradiol levels.

The second drawback of the study was the lack of parity data. Increased parity has been reported to be associated with increased breast cancer risk. We also did not collected data on age at menarche, age at menopause and age at first labour. Finally, the difference in age between postmenopausal patients and controls might be a reason for the significant difference in adiponectin (Table 5).

**Table 5. Mann-Whitney U test of the mean values in the postmenopausal group. $N_{patients}=23$; $N_{controls}=25$**

| | BMI | Age | TG | TC | HDL | LDL | FSG | HOMA-IR | Adiponectin |
|---|---|---|---|---|---|---|---|---|---|
| **Z** | -0.341 | -4.163 | -0.898 | -0.237 | -1.239 | -0.527 | -1.591 | -2.404 | -2.322 |
| **p** | 0.733 | 0.000 | 0.369 | 0.812 | 0.215 | 0.599 | 0.112 | 0.016 | 0.020 |
| **OR** | - | 1.206 (1.07-1.35) | - | - | - | - | - | 0.843 (0.49-1.44) | 0.755 (0.59-0.97) |
| | - | <0.001 | - | - | - | - | - | - | - |

TC: Total cholesterol, FSG: fasting serum glucose, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, HOMA-IR: homeostatic model assessment for insulin resistance, OR: odds ratio, TG: triglyceride

**Table 6. Distribution of the patient and control groups by adiponectin levels**

| | | Group | | | | |
|---|---|---|---|---|---|---|
| | **Patient** | | **Control** | | | |
| | n | % of row | n | % of row | p | |
| **Adiponectin** | 3-5.9 mg/L | 45 | 57.0 | 34 | 43.0 | 0.325 |
| | 6-8.9 | 8 | 72.7 | 3 | 27.3 | - |
| | 9 and above | 6 | 42.9 | 8 | 57.1 | - |

**Table 7. Comparison of serum adiponectin/body mass index (mg • $m^2$/ kg • L) levels in sub-groups of breast cancer classified according to histopathological examination of CerbB2 immunostaining pattern, $N_{patients}=52$**

| | CerbB2 negative (N=42) | CerbB2 positive (N=10) | p |
|---|---|---|---|
| Adiponectin/BMI (mg • $m^2$/kg • L) | 0.149 (0.127-0.210) | 0.174 (0.138-0.250) | 0.390 |

BMI: Body mass index

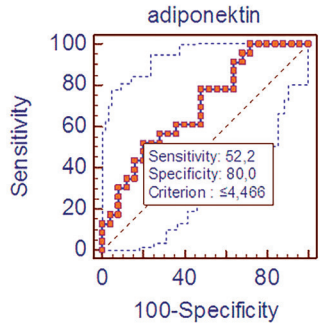


**Figure 4.** Plot of serum adiponectin levels in postmenopausal group, $N_{patients}$=23; $N_{controls}$=25 (AUC: 70%)

AUC: Area under the curve

## Conclusion

The postmenopausal patients showed significantly lower levels of serum adiponectin than the controls (Figure 1, Table 5). Our results also support previous studies that this significant difference exists irrespective of BMI (Table 4). Although the number of samples was not sufficient, we calculated a serum adiponectin level of 4.6 mg/L, below which postmenopausal cases would be more likely to have breast cancer, and this model provided a reasonable AUC with great specificity. However, the sensitivity of this model was quite low (Figure 4).

Although breast cancer has been shown in several studies to be an obesity-related disease (7,8,11), our study found no significant correlation with HOMA-IR, BMI or with any of the other parameters. Values of HOMA-IR and BMI were not found to be higher in the patient group compared to the controls (Table 7); in fact, patients had lower HOMA-IR compared to controls in the postmenopausal group. Cerb-B2 expression was not associated with serum adiponectin.

We concluded that lower adiponectin and higher age at diagnosis are risk factors for postmenopausal breast cancer. Although an analysis by comparing the tertiles of adiponectin against the patient and control groups yielded no significant difference, a level of serum adiponectin below 4.46 mg/L may be associated with breast cancer risk. We think that if parameters like waist circumference, serum oestradiol level, parity, age at menarche, age at first labour, including histological and imaging findings (magnetic resonance, mammography, ultrasonography, positron emission tomography, etc) are properly evaluated with a larger sample size, more distinctive results may be achieved, fortifying the value of serum adiponectin levels in the early diagnosis of breast cancer.

### Ethics

**Ethics Committee Approval:** This study was conducted in compliance with the Good Clinical Practice guidelines and the ethical principles stated in the Declaration of Helsinki, and was approved by the ethical committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital under report numbered 469.

**Informed Consent:** All the patients gave written consent to participate in the study.

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

**Authorship Contributions:** Surgical and Medical Practices - D.C.T.; Concept - T.A.; Design - H.A., T.A.; Data Collection or Processing - D.C.T., C.K.T.; Analysis or Interpretation - T.A., E.S., C.K.T.; Literature Search - T.A.; Writing - T.A.

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

**Financial Disclosure:** Grant support on ELISA reagents by University of Health Sciences Turkey, İstanbul Training and Research Hospital.

## References

1. WHO incidence. [Online] Available from: URL: https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/.
2. GLOBOCAN 2008. [Online] Available from URL: https://www.iarc.fr/wp-content/uploads/2018/07/GLOBOCAN2008.pdf.
3. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M, Comparative risk assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors Lancet 2005; 366; 1784-93.
4. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to Clq, produced exclusively in adipocytes. J Biol Chem 1995; 270: 26746-9.
5. Vona-Davis L, Rose DP. Angiogenesis, adipokines and breast cancer. Cytokine Growth Factor Rev 2009; 20: 193-201.
6. Dalamaga M. Obesity, insulin resistance, adipocytokines and breast cancer: New biomarkers and attractive therapeutic targets. World J Exp Med 2013; 3: 34-42.
7. Avgerinos K, Spyrou N, Mantzoros C, Dalamaga M. Obesity and Cancer Risk: Emerging biological mechanisms and perspective. Metabolism 2019; 92: 121-35.
8. Spyrou N., Avgerinos K., Mantzoros C., Dalamaga M. Classic and novel adipocytokines at the intersection of obesity and cancer: diagnostic and therapeutic strategies. Curr Obes Rep 2018; 7: 260-75.
9. Karaduman M, Bilici A, Ozet A, Sengul A, Musabak U, Alomeroglu M. Tissue levels of adiponectin in breast cancer patients. Med Oncol 2007; 24: 361-6.
10. Chen DC, Chung YF, Yeh YT, Chaung HC, Kuo FC, Fu OY, et al. Serum adiponectin and leptin levels in Taiwanese breast cancer patients. Cancer Lett 2006; 237: 109-14.
11. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab 2004; 89: 1102-7.
12. Körner A, Pazaitou-Panayiotou K, Kelesidis T, Kelesidis I, Williams CJ, Kaprara A, et al. Total and high-molecular-weight adiponectin in breast cancer: in vitro and in vivo studies. J Clin Endocrinol Metab 2007; 92: 1041-8.
13. Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer. Endocr Rev 2012; 33: 547-94.
14. Ahn J, Schatzkin A, Lacey JV Jr, Albanes D, Ballard-Barbash R, Adams KF, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. Arch Intern Med 2007; 167: 2091-102.
15. Emaus MJ, van Gils CH, Bakker MJ, Bisschop CNS, Monninkhof EM, de Mesquita HBB, et al. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. Int J Cancer 2014; 135: 2887-99.
16. Rosner B, Eliassen AH, Toriola AT, Chen WY, Hankinson SE, Willett WC, et al. Weight and weight changes in early adulthood and later breast cancer risk. Int J Cancer 2017; 140: 2003-14.
17. Chen Y, Liu L, Zhou Q, Imam MU, Cai J, Wang Y, et al. Body mass index had different effects on premenopausal and postmenopausal breast cancer

risks: a dose-response meta-analysis with 3,318,796 subjects from 31 cohort studies. BMC Public Health 2017; 17: 936.

18. Brochu-Gaudreau K, Rehfeldt C, Blouin R, Bordignon V, Murphy BD, Palin MF. Adiponectin action from head to toe. Endocrine 2010; 37: 11-32.
19. Kishida K, Funahashi T, Shimomura I. Adiponectin as a routine clinical biomarker Best Pract Res Clin Endocrinol Metab 2014 ; 28: 119-30.
20. Hivert MF, Sullivan LM, Fox CS, Nathan DM, D'Agostino sr RB, Wilson PWF, et al. Associations of adiponectin, resistin, and tumor necrosis factor-α with insulin resistance J Clin Endocrinol Metab 2008; 93: 3165-72.
21. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930-5.
22. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 2003; 95: 1218-26.
23. Zeleniuch-Jacquotte A, Afanasyeva Y, Kaaks R, Rinaldi S, Scarmo S, Liu M, et al. Premenopausalserum androgens and breast cancer risk: a nested case-control study. Breast Cancer Res 2012; 14: R32.
24. Cubukcu E, Olmez F, Kanat O, Kabul S, Canhoroz M, Avci N, et al. Lack of prognostic significance of adiponectin immunohistochemical expression in patients with triple-negative breast cancer Contemp Oncol (Pozn) 2014; 18: 34-8.
25. Gu L, Cao C, Fu J, Li Q, Li DH, Chen MY. Serum adiponectin in breast cancer: A meta-analysis. Medicine (Baltimore) 2018; 97: e11433.
26. Ma HQ, Cui LH, Li CC, Yu Z, Piao JM. Effects of Serum Triglycerides on prostate cancer and breast cancer risk: a meta-analysis of prospective studies. Nutr Cancer 2016; 68: 1073-82.
27. Li X, Liu Z, Wu H, Dai W, Arshad B, Xu Z, et al. Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy. Lipids Health Dis 2018; 17: 91.

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# Evaluation of Plateletcrit and Neutrophil/Lymphocyte, Monocyte/Lymphocyte and Platelet/Lymphocyte Ratios in Endometrial Polyp

## Endometriyal Polipte Plateletkrit, Nötrofil/Lenfosit, Monosit/Lenfosit ve Platelet/Lenfosit Oranlarının Değerlendirilmesi

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## ABSTRACT

**Introduction:** To evaluate the association between endometrial polyp (EP) and inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR) and plateletcrit (PCT).

**Methods:** In this retrospective and comparative case series, a total of 137 patients who had undergone endometrial biopsy due to various causes were included. Forty-eight of these patients were diagnosed with EP and classified as the patient group. Eighty-nine patients were diagnosed with proliferative/secretory endometrium and classified as the control group. The groups' PCT, NLR, PLR and MLR values were compared as statistically.

**Results:** There was no significant difference between the EP and control groups in terms of the NLR, PLR and MLR and the PCT value.

**Conclusion:** This is the first study in the literature evaluating the relationship between NLR, PLR and MLR and PCT value and EP. Further large-scale studies are essential to determine the exact role of NLR, PLR and MLR and PCT value on EPs.

**Keywords:** Endometrial diseases, polyps, blood cell count

## ÖZ

**Amaç:** Endometriyal polip (EP) ile nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), monosit/lenfosit oranı (MLO) ve plateletkrit (PCT) gibi enflamasyon belirteçleri arasındaki ilişkiyi değerlendirmektir.

**Yöntemler:** Bu retrospektif karşılaştırmalı olgu serisine, çeşitli nedenlerle endometriyal biyopsi yapılan toplam 137 hasta dahil edildi. Bu hastaların 48'i EP tanısını alarak hasta grubu olarak sınıflanırken 89 hasta proliferatif/sekretuvar endometrium tanısı alarak kontol grubu olarak sınıflandı. Grupların NLO, PLO, MLO ve PCT değerleri istatistiksel olarak karşılaştırıldı.

**Bulgular:** EP ve kontrol grupları arasında NLO, PLO, MLO ve PCT değerleri açısından anlamlı fark saptanmadı.

**Sonuç:** Bu çalışma; NLO, PLO, MLO ve PCT değerleri ile EP arasındaki ilişkiyi irdeleyen ilk çalışmadır. NLO, PLO, MLO ve PCT değerlerinin EP'deki rolünü belirlemek için geniş katılımlı çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Endometriyal hastalıklar, polipler, kan hücresi sayımı

## Introduction

Endometrial polyp (EP) is a frequent disease of the endometrium, characterised by a localised hyperplastic over growth of endometrial glands and stroma around a vascular core and the presence of inflammatory cells in the stroma (1). Although the etiopathogenesis has not been fully elucidated, oestrogen and progesterone, apoptosis, growth factors, metabolism and ageing, selective oestrogen receptor modulators, hormone replacement therapy, Ki-67 and also endometrial inflammation may play a role in its etiopathogenesis (2,3).

Although many EPs are asymptomatic, abnormal uterine bleeding is the most common symptom of EP. Even though transvaginal ultrasonography (TVUSG) provides reliable data for the diagnosis of EP, hysteroscopy is the gold standard diagnostic procedure that is also simultaneously used for treatment.

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR) and plateletcrit (PCT) in peripheral blood are values that are simple to calculate, have a very low cost and can reveal the systemic inflammation.

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There is no study in the literature that evaluates the relationship between NLR, PLR and MLR and PCT value and EP. In this study, we aimed to investigate the association between symptomatic EPs without ultrasonographic EP-compatible views and inflammation markers (NLR, PLR, MLR and PCT).

## Methods

In this retrospective and comparative case series, a total of 137 patients who had undergone endometrial biopsy due to various causes between June 2017 and March 2019 at Zonguldak Maternity and Child Health Hospital were evaluated. This study was approved by the Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University, Turkey (protocol no: 2019-75-08/05, date: 08.05.2019). Patients' consent was not obtained because the study was retrospective. Forty-eight of these patients were diagnosed with EP and classified as the patient group. EP-compatible views such as dilated glands filled with proteinaceous fluid or a hyperechogenic lesion with regular contours were not detected on ultrasonography prior to the endometrial biopsy. Eighty-nine patients were diagnosed with proliferative/secretory endometrium and classified as the control group. Patient with a history of malignancy, pelvic inflammatory disease, severe liver, kidney and cardiac disease, chronic inflammatory disease and those who received hormone replacement therapy were excluded. Patients' demographic characteristics, pathology results and laboratory values were extracted from the automation system of the hospital. PCT, neutrophil count, lymphocyte count, monocyte count, platelet count values were obtained from complete blood cell count parameters within a month before the endometrial biopsy. PLR value was calculated by dividing the platelet count by the number of lymphocytes. NLR value was calculated by dividing the neutrophil count by the number of lymphocytes and MLR value was calculated by dividing the monocyte count by the number of lymphocytes. The groups' PCT, NLR, PLR and MLR values were compared statistically.

### Statistical Analysis

IBM SPSS 22.0 (IBM SPSS Statistics, IL, USA) was used for all the statistical analyses. Data distribution was determined using the Kolmogorov-Smirnov test. Continuous variables were expressed as means ± standard deviations and categorical variables as frequencies and percentages. Continuous variables were compared by an independent sample t-test or Mann-Whitney U test. $p<0.05$ was considered significant for all the tests.

## Results

The mean age of the 48 patients diagnosed as EP was 45.5±8.9 and the mean age of the 89 patients diagnosed as proliferative/secretory endometrium was 43.4±6.3. There was no significant difference in the terms of age between the two groups (p=0.158). Endometrial biopsy was performed in 39 patients with abnormal uterine bleeding, 3 patients with postmenopausal increased endometrial thickness, 4 patients with endometrial irregularity and 2 patients with postmenopausal bleeding in the EP group. In the control group, all the patients had undergone endometrial biopsy due to abnormal uterine bleeding. The blood cell count data of the EP and control groups are shown in Table 1. Neutrophil, lymphocyte, monocyte and platelet count of the groups were not significantly different. NLR, PLR and MLR of the EP group was 2.32±1.46, 137.14±66.40 and 0.20±0.13 and in the control group was 2.72±3.58, 135.05±62.44 and 0.20±0.26, respectively. The PCT value in the EP group was 0.22±0.05 and in the control group was 0.22±0.05. There was no significant difference between the two groups in terms of the NLR, PLR and MLR and PCT value (p=0.458, p=0.856, p=0.995, p=0.963) (Table 1).

## Discussion

EP is one of the causes of abnormal uterine bleeding. They are usually benign, but can have premalignant or malignant tissue variations. Polyps are rare before 30 years and peak in the postmenopausal period (4). Increased fibrotic tissue compared to the normal endometrium, thick-walled blood vessels and inflammatory cells like polymorphonuclear leucocytes, lymphocytes and plasma cells in the stroma are pathologic features of EP (1).

The etiopathogenesis of EP remains unclear. Some studies reported that cytokines like cyclooxygenase, interferon-gamma, aromatase and matrix metalloproteinases can cause EP by causing angiogenesis and cell proliferation (5,6). Some investigators showed that EP is formed as a result of an imbalance in the expression of oestrogen and progesterone receptors (7,8) and deficient apoptosis through the loss of the regulation of Bcl-2 and Ki-67 (9,10). The endometrial inflammatory state can stop the apoptosis in the endometrium and may cause EPs. Endometritis, endometriosis, adenomyosis are examples of pro-inflammatory states (2).

NLR, PLR, MLR and PCT are systemic inflammatory response markers and are associated with several diseases such as peripheral vascular

**Table 1. Neutrophil, lymphocyte, monocyte, platelet and PCT count, NLR, PLR and MLR values in the endometrial polyp and control groups**

| | Endometrial polyp | Control group | p |
|---|---|---|---|
| Neutrophil (µL) | 0.36±0.14 | 0.35±0.15 | 0.294 |
| Lymphocyte (µL) | 2.13±0.91 | 2.06±0.70 | 0.635 |
| Monocyte (µL) | 4.11±2.07 | 4.72±1.73 | 0.805 |
| Platelet (K/µL) | 250.21±66.10 | 254.20±62.10 | 0.728 |
| PCT (%) | 0.22±0.05 | 0.22±0.05 | 0.963 |
| NLR | 2.32±1.46 | 2.72±3.58 | 0.458 |
| PLR | 137.14±66.40 | 135.05±62.44 | 0.856 |
| MLR | 0.20±0.13 | 0.20±0.26 | 0.995 |

PCT: Plateletcrit, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MLR: monocyte/lymphocyte ratio

disease, coronary artery disease, malignancies, rheumatoid arthritis and ulcerative colitis (11-15).

Recurrent pregnancy loss is defined as 3 consecutive pregnancy losses prior to 20 weeks of gestation. The aetiology of 50% of recurrent pregnancy loss is unexplained, but inflammation and coagulation disorders play a significant role. In a study with 208 patients who had 2 or more first trimester spontaneous abortions; white blood cell, platelet, lymphocyte and neutrophil count, red cell distribution width, PCT and NLR in the recurrent pregnancy loss group were significantly higher than in the control group (16).

Nasal polyp is characterised by progressive inflammation with eosinophil, T-cell, neutrophil and plasma cell. The study by Atan et al. (17) included 105 patients diagnosed as nasal polyp. In the nasal polyp group, the mean NLR value was significantly (p=0.001) higher than in the control group, while there was no significant difference in the mean PLR value.

Endometriosis is identified using ectopic endometrial tissue. It is a chronic inflammatory condition associated with findings related to inflammation like dyspareunia, dysmenorrhoea and chronic pain. Aydın (18) (187 patients), Kim et al. (19) (219 patients) and Yavuzcan et al. (20) (33 patients) reported that there is no relationship between NLR and endometrioma. On the other hand, in studies by Cho et al. (21) including 231 patients and Tokmak et al. (22) including 467 patients, NLR was found to be elevated in endometriosis cases. Furthermore, in Aydın's (18) study, PLR value in the endometrioma group was higher than in the benign cyst group, but in another study (23), there was no difference in PLR value between the two groups.

EP typically appears as cystic spaces corresponding to dilated glands filled with proteinaceous fluid or a hyperechogenic lesion with regular contours on TVUSG. EP can also be seen as a focal mass or nonspecific thickening. These findings are not specific to EP. The addition of power Doppler can enhance the diagnostic efficacy of TVUSG. Saline infusion sonography improves the diagnostic accuracy. Hysteroscopic-guided biopsy provides the highest sensitivity and specificity for the diagnosis of EP (24). Although blind endometrial biopsy has a high sensitivity and positive pressure ventilation, this technique can cause polyp fragmentation and the inaccurate diagnosis of EP (25).

EPs are generally asymptomatic. In a population-based Danish study, EP was significantly more frequent in asymptomatic women compared to women with abnormal uterine bleeding (26). Abnormal uterine bleeding is the most common symptom for the symptomatic EP (24). In a study by Kanthi et al. (27), 75.6% of premenopausal women and 47.7% of postmenopausal women with polyps had abnormal uterine bleeding. In another study, 20% of postmenopausal women with polyp and 76.3% of premenopausal women were symptomatic with abnormal uterine bleeding (28).

In our study, we evaluated the association between the NLR, PLR and MLR and PCT value and symptomatic EP without ultrasonographic EP-compatible views. These patients were diagnosed by endometrial biopsy, but blind endometrial biopsy is inaccurate in diagnosing EP. If we could find a significant relationship between the two groups; NLR, PLR and MLR and PCT value, which are simple to calculate and cheap, could have been effective in evaluating the diagnosis of EP before biopsy Thus, additional tests such as saline infusion sonography, Doppler ultrasonography and hysteroscopy before blind biopsy can be done.

## Conclusion

There are inconsistent conclusions in the literature about NLR, PLR and MLR and PCT value in various diseases. Also, to the best of our knowledge, this is the first study in the literature appraising the association between NLR, PLR and MLR and PCT value and EPs. In our study, there was no significant difference between the symptomatic EPs without ultrasonographic EP-compatible views group and the control group in terms of the NLR, PLR and MLR and PCT value. Further large-scale studies are essential to determine the exact role of NLR, PLR and MLR and PCT value on EPs.

### Ethics

**Ethics Committee Approval:** This study was approved by the Local Ethics Committee of Zonguldak Bülent Ecevit University, Turkey (protocol no: 2019-75-08/05, date: 08.05.2019).

**Informed Consent:** Patients' consent was not obtained because the study was retrospective.

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

**Authorship Contributions:** Surgical and Medical Practices - A.T.Ç., İ.Ş.Ö.; Concept - A.T.Ç., İ.Ş.Ö.; Design - A.T.Ç.; Data Collection or Processing - A.T.Ç.; Analysis or Interpretation - A.T.Ç., İ.Ş.Ö.; Literature Search - A.T.Ç.; Writing - A.T.Ç.

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## References

1. Buckley CH. Normal endometrium and non-proliferative conditions of the endometrium. Fox H, Wells M, editors. Obstetrical and Gynaecological Pathology. 5th ed. London: Churchill Livingstone; 2002.p.416-7.
2. Indraccolo U, Di Iorio R, Matteo M, Corona G, Greco P, Indraccolo SR. The pathogenesis of endometrial polyps: a systematic semi-quantitative review. Eur J Gynaecol Oncol 2013; 34: 5-22.
3. Deligdisch L. Hormonal pathology of the endometrium. Mod Pathol 2000; 13: 285-94.
4. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol 2009; 33: 102-8.
5. Inagaki N, Ung L, Otani T, Wilkinson D, Lopata A. Uterine cavity matrix metalloproteinases and cytokines in patients with leiomyoma, adenomyosis or endometrial polyp. Eur J Obstet Gynecol and Reprod Biol 2003;111:197-203.
6. Erdemoglu E, Güney M, Karahan N, Mungan T. Expression of cyclooxygease-2, matrix metalloproteinase-2 and matrix metalloproteinase-9 in premenopausal and postmenopausal endometrial polyps. Maturitas 2008; 59: 268-74.
7. Lopes RG, Baracat EC, de Albuquerque Neto LC, Ramos JFD, Yatabe S, Depesr DB, et al. Analysis of estrogen- and progesterone-receptor expression in endometrial polyps. J Minim Invasive Gynecol 2007; 14: 300-3.

8. Mittal K, Schwartz L, Goswami S, Demopoulos R. Estrogen and progesterone receptor expression in endometrial polyps. Int J Gynecol Pathol 1996; 15: 345-8.

9. Taylor LJ, Jackson TL, Reid JG, Duffy SR. The differential expression of oestrogen receptors, progesterone receptors, Bcl-2 and Ki67 in endometrial polyps. BJOG 2003; 110: 794-8.

10. McGurgan P, Taylor LJ, Duffy SR, O'Donovan PJ. Are endometrial polyps from pre-menopausal women similar to post-menopausal women? An immunohistochemical comparison of endometrial polyps from pre- and post-menopausal women. Maturitas 2006; 54: 277-84.

11. Fan Y, Li X, Zhou XF, Zhang DZ, Shi XF. [Value of neutrophil lymphocyte ratio in predicting hepatitis B-related liver failure]. Zhonghua Gan Zang Bing Za Zhi 2017; 25: 726-31.

12. Sönmez O, Ertaş G, Bacaksız A, Tasal A, Erdoğan E, Asoğlu E, et al. Relation of neutrophil-to-lymphocyte ratio with the presence and complexity of coronary artery disease: an observational study. Anadolu Kardiyol Derg 2013; 13: 662-7.

13. Celikbilek M, Dogan S, Ozbakır O, Zararsız G, Kücük H, Gürsoy S, et al. Neutrophil-lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal 2013; 27: 72-6.

14. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med 2012; 5: 2.

15. Tousoulis D, Antoniades C, Koumallos N, Stefanadis C. Proinflammatory cytokines in acute coronary syndromes: from bench to bedside. Cytokine Growth Factor Rev 2006; 17: 225-33.

16. Aynıoglu O, Isık H, Sahbaz A, Harma MI, Isık M, Kokturk F. Can Plateletcrit be a Marker for Recurrent Pregnancy Loss? Clin Appl Thromb Hemost 2016; 22: 447-52.

17. Atan D, Özcan KM, Köseoğlu S, İkincioğulları A, Çetin MA, Ensari S, et al. Nazal polipte yeni öngörücü parametreler: Nötrofil lenfosit oranı ve trombosit lenfosit oranı. Kulak Burun Bogaz Ihtis Derg 2015; 25: 97-101.

18. Aydın DS. Diagnostic Performance of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Endometrioma. Istanbul Med J 2019; 20: 13-6.

19. Kim SK, Park JY, Jee BC, Suh CS, Kim SH. Association of the neutrophil-to-lymphocyte ratio and CA 125 with the endometriosis score. Clin Exp Reprod Med 2014; 41: 151-7.

20. Yavuzcan A, Cağlar M, Ustün Y, Dilbaz S, Ozdemir I, Yıldız E, et al. Evaluation of mean platelet volume, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in advanced stage endometriosis with endometrioma. J Turk Ger Gynecol Assoc 2013; 14: 210-5.

21. Cho S, Cho H, Nam A, Kim HY, Choi YS, Park KH, et al. Neutrophil-to-lymphocyte ratio as an adjunct to CA-125 for the diagnosis of endometriosis. Fertil Steril 2008; 90: 2073-9.

22. Tokmak A, Yildirim G, Öztaş E, Akar S, Erkenekli K, Gülşen P, et al. Use of neutrophil-to-lymphocyte ratio combined with ca-125 to distinguish endometriomas from other benign ovarian cysts. Reprod Sci 2016; 23: 795-802.

23. Viganò P, Ottolina J, Sarais V, Rebonato G, Somigliana E, Candiani M. Coagulation status in women with endometriosis. Reprod Sci. 2017 Jul 6. doi: 10.1177/1933719117718273. [Epub ahead of print].

24. American Association of Gynecologic Laparoscopists. AAGL practice report: practice guidelines for the diagnosis and management of endometrial polyps. J Minim Invasive Gynecol 2012; 19: 3-10.

25. Hamou J. Hysteroscopy and Microcolopohysteroscopy: Text and Atlas. Norwalk: Appleton & Lange; 1991.

26. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol 2009; 33: 102-8.

27. Kanthi JM, Remadevi C, Sumathy S, Sharma D, Sreedhar S, Jose A. Clinical Study of Endometrial Polyp and Role of Diagnostic Hysteroscopy and Blind Avulsion of Polyp. J Clin Diagn Res 2016; 10: QC01-4.

28. Preutthipan S, Herabutya Y. Hysteroscopic polypectomy in 240 premenopausal and postmenopausal women. Fertility Sterility 2005; 83: 705-9.

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# Evaluation of Ventricular Repolarisation Features with Novel Electrocardiographic Parameters in Patients with Severe Periodontitis

## Şiddetli Periodontitisli Hastalarda Ventriküler Repolarizasyon Özelliklerinin Yeni Elektrokardiyografik Parametrelerle Değerlendirilmesi

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## ABSTRACT

**Introduction:** Ventricular arrhythmic predictors in severe periodontitis may be linked with cardiovascular events and the sudden death risk. In this study, we evaluated certain electrocardiographic (ECG) ventricular arrhythmic predictors in patients with severe periodontitis.

**Methods:** ECG parameters of 72 patients diagnosed with severe periodontitis, which are indicative of ventricular arrhythmia, were examined, and these parameters were compared with the control group.

**Results:** Compared to the control group, QT interval (QT) (p=0.014), corrected QT (QTc) (p<0.001), QT dispersion (QTd) (p<0.001), QTdc p<0.001), JT interval (p=0.012), JTc interval (p<0.001), T peak and end interval (Tp-e) (p<0.001), Tp-e/QT ratio (p<0.001), Tp-e/QTc ratio (p<0.001), Tp-e/JT ratio (p<0.001) and Tp-e/JTc ratio (<0.001) were found to be higher in patients with severe periodontitis.

**Conclusion:** Our study showed that arrhythmic ECG markers were significantly prolonged in patients with severe periodontitis. In future extensive prospective studies, we think that these arrhythmic predictors should be evaluated to predict malignant arrhythmias.

**Keywords:** Arrhythmia, electrocardiography, periodontitis, JTc interval, Tp-e/QTc ratio

## ÖZ

**Amaç:** Şiddetli periodontitiste ventriküler aritmik prediktörler kardiyovasküler olaylar ve ani ölüm riski ile ilişkili olabilir. Bu çalışmada şiddetli periodontitisli hastalarda bazı elektrokardiyografik (EKG) ventriküler aritmik prediktörler değerlendirilmiştir.

**Yöntemler:** Şiddetli periodontitis tanısı alan 72 hastanın, ventriküler aritminin göstergesi olan EKG parametreleri incelendi ve bu parametreler kontrol grubuyla karşılaştırıldı.

**Bulgular:** Kontrol grubu ile karşılaştırıldığında, şiddetli periodontitisli hastalarda QT aralığı (p=0,014), düzeltilmiş QT aralığı (QTc) (p<0,001), QT dağılım aralığı (QTd) (p<0,001), QTdc aralığı p<0,001), JT aralığı (p=0,012), JTc aralığı (p<0,001), T tepe ve bitiş aralığı (Tp-e) (p<0,001), Tp-e/QT oranı (p<0,001), Tp-e/QTc oranı (p<0,001), Tp-e/JT oranı (p<0,001) ve Tp-e/JTc oranı (<0,001) daha yüksek bulundu.

**Sonuç:** Araştırmamız, şiddetli periodontitisli hastalarda aritmik EKG belirteçlerin anlamlı şekilde uzadığını göstermiştir. Gelecekteki kapsamlı prospektif çalışmalarda, bu aritmik belirleyicilerin malign aritmileri öngörmek için değerlendirileceğini düşünüyoruz.

**Anahtar Kelimeler:** Aritmi, elektrokardiyografi, periodontitis, JTc aralığı, Tp-e/QTc oranı

## Introduction

Periodontitis is a chronic inflammatory periodontal disease that gradually destroys the supporting structures of the teeth, affecting approximately 50% of the adult population (1). The harmful influences of periodontitis are not only restricted to the oral cavity, but it also affects general health (2). Classification of periodontitis is based on stages defined by the severity, complexity, and distribution (Table 1).

There is consistent and potent epidemiological evidence that periodontitis increases the risk of cardiovascular disease [(CVD); for example, atherosclerosis with different mechanisms] (5).

Electrical changes in the heart throughout ventricular repolarisation can cause fatal rhythm disturbances (6). Myocardial depolarisation and repolarisation have been assessed using various methods. QT interval (QT), QT dispersion (QTd) and corrected QT (QTc) have been linked with ventricular arrhythmic conditions and sudden death (7).

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In recent years, JT, JTc, T peak and end interval (Tp-e) and Tp-e/QT and Tp-e/QTc proportions have also shown to be different parameters indicating fatal ventricular arrhythmias (8).

In this study, we aimed to explore the influence of severe periodontitis on cardiac ventricular arrhythmic abnormalities.

## Methods

### Study Population

Electrocardiogram (ECG) recordings of 72 patients with periodontitis who were received in the University of Bolu Abant İzzet Baysal Department of Periodontology between July 2018 and December 2018 were cross-sectionally analysed and compared with controls. The study was conducted after obtaining ethical approval from the Bolu Abant İzzet Baysal University Ethics Committee (decision number: 2019/264, date: 21/11/2019).

The study was conducted in compliance with the ethical principles according to the Declaration of Helsinki.

Patients were diagnosed as having periodontitis or were declared to be periodontally healthy based on the criteria proposed by the International Workshop for the Classification of Periodontal Diseases and Conditions in 2017 (1). All patients agreed to participate in the study and gave their written informed consent.

### Exclusion Criteria

Participants with a history of diabetes, smoking, hypertension, hyperlipidaemia, structural heart disease, atherosclerotic CVDs (coronary artery disease, etc), ejection fraction <50%, electrolyte imbalances, liver failure, thyroid disorders, renal failure, malignancies, chronic lung disease, or any other systemic illness were excluded. Besides, patients over 45 years old were excluded because of the reduced risk of an arrhythmic event with ageing. Participants with a history of ventricular arrhythmias, atrial fibrillation (AF), and those having left-axis deviation, ST-segment depression, and hypertrophic findings on ECG were also excluded, because of the possible influences of these ECG differences on the computed ECG parameters.

**Table 1. The 2017 workshop on the classification of periodontal and peri-implant diseases and conditions (1)**

| Stages: Based on the severity (3) and complexity of management (4) | |
|---|---|
| **Stage I** | Initial periodontitis |
| **Stage II** | Moderate periodontitis |
| **Stage III** | Severe periodontitis with potential for additional tooth loss |
| **Stage IV** | Severe periodontitis with potential for loss of the dentition |

### Electrocardiography

The 12-lead ECG was recorded with the Nihon Kohen Cardiofax ECG-1950 VET device. Two cardiologists, blinded to the data, performed the ECG measurements and calculations manually with the TorQ 150 mm digital caliper LCD device. QT interval was measured, beginning from the initiation of the QRS duration to the end of the T wave. JT interval was measured from the end of the QRS complex to the end of the T wave. QTd was defined as being the difference between the maximum and minimum QT intervals measured at different leads. The Tp-e range is the range from the peak of the T wave to the end of the T wave. QTc, QTdc and JTc were calculated using the Bazett's formula (QTc= QT/√RR) (9). Besides, the rates of these intervals calculated, the differences between intra-observer and inter-observer measurements were below 5 percent.

### Statistical Analysis

Analyses were conducted using the SPSS 21.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA). Mean ± standard deviation was used for quantitative variables, and numbers and percentages were used to express qualitative variables. In independent groups, the chi-square test was used for qualitative variables, and the Student t-test was used for quantitative variables. A p value less than 0.05 was considered statistically significant.

## Results

The baseline characteristics of the study and control groups were similar (Table 2).

Compared to the control group, QT interval (376.7±21.4 vs. 362.3±27.0 ms, p=0.014), QTc (404.4±24.2 vs 381.0±16.7 ms, p<0.001), QTd (26.5±11.2 vs. 18.0±5.9 ms, p<0.001), QTdc (28.6±12.0 vs 18.9±5.7 ms, p<0.001), JT interval (293.0±39.2 vs 272.4±27.2 ms, p=0.012), JTc interval (312.9±22.6 vs 286.1±18.3 ms, p<0.001), Tp-e interval (106.9±12.0 vs. 73.6±7.4 ms, p<0.001), Tp-e/QT ratio (0.28±0.03 vs 0.20±0.03, p<0.001), Tp-e/QTc ratio (0.27±0.04 vs 0.19±0.02, p<0.001), Tp-e/JT ratio (0.37±0.05 vs 0.27±0.03, p<0.001) and Tp-e/JTc ratio (0.34±0.04 vs 0.26±0.03, p<0.001), were found to be higher in patients with severe periodontitis (Table 3), (Figure 1).

## Discussion

In our study, we showed that periodontitis is significantly linked with arrhythmic predictors. To the best of our knowledge, there is no other study investigating cardiac ventricular markers in periodontitis patients.

Periodontitis is an increasing epidemic health problem that has been thought to be a risk factor for myocardial infarction (10). Although

**Table 2. General characteristics of the study groups**

| Baseline characteristics | Severe periodontitis Mean ± SD (n=72) | Control group Mean ± SD (n=72) | p |
|---|---|---|---|
| **Age (years)** | 35.4±6.7 | 33.5±6.4 | 0.222 |
| **Male/female** | 56/16 | 46/26 | 0.200 |
| **BMI** | 25.5±3.4 | 25.3±3.2 | 0.842 |

BMI: Body mass index, SD: standard deviation

**Table 3. Electrocardiographic findings of the study population**

| | Severe periodontitis Mean ± SD (n=72) | Control group Mean ± SD (n=72) | p |
|---|---|---|---|
| **Heart rate (bpm)** | 70.4±13.7 | 67.5±11.6 | 0.328 |
| **QT ms** | 376.7±21.4 | 362.3±27.0 | 0.014 |
| **QTc ms** | 404.4±24.2 | 381.0±16.7 | <0.001 |
| **QTd ms** | 26.5±11.2 | 18.0±5.9 | <0.001 |
| **QTdc ms** | 28.6±12.0 | 18.9±5.7 | <0.001 |
| **QRS ms** | 94.8±10.2 | 90.6±7.6 | 0.051 |
| **JT ms** | 293.0±39.2 | 272.4±27.2 | 0.012 |
| **JTc ms** | 312.9±22.6 | 286.1±18.3 | <0.001 |
| **Tp-e ms** | 106.9±12.0 | 73.6±7.4 | <0.001 |
| **Tp-e/QT** | 0.28±0.03 | 0.20±0.03 | <0.001 |
| **Tp-e/QTc** | 0.27±0.04 | 0.19±0.02 | <0.001 |
| **Tp-e/JT** | 0.37±0.05 | 0.27±0.03 | <0.001 |
| **Tp-e/JTc** | 0.34±0.04 | 0.26±0.03 | <0.001 |

Bpm: Beat per minute, ms: millisecond, QT interval: from the beginning of the QRS complex to the end of the T wave, QTc: corrected QT interval, QTd: QT dispersion: the difference between the maximum and minimum QT intervals, QTdc: corrected QT dispersion, Tp-e: T peak and end interval, JT interval (JT): from the end of the QRS complex (J point) to the end of the T wave, JTc: corrected JT interval, SD: standard deviation

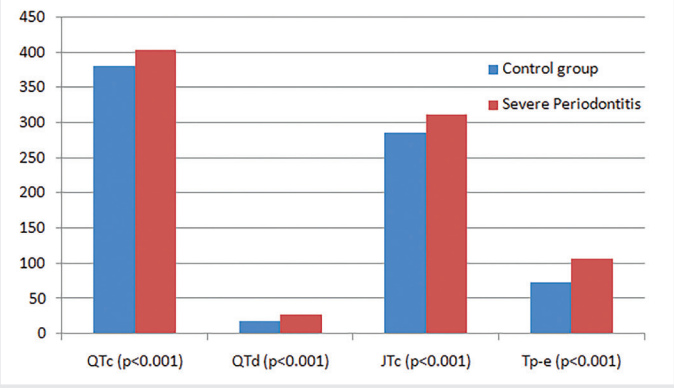


**Figure 1.** QTc, QTd, JTc and Tp-e distributions of the control and severe periodontitis groups

QTc: Corrected QT interval, QTd: difference between the maximum and minimum QT intervals, JTc: corrected JT interval, Tp-e: T peak and end interval

patients with periodontitis are successfully treated, life-long supportive care is recommended for these patients (11). The systematic inflammatory response leads to endothelial dysfunction, and endothelial dysfunction also contributes to CVDs (12), especially electrocardiographic anomalies that are sensitive predictors of lethal coronary heart disease (CHD), and are significantly linked to subsequent death from CHD (13). In the literature, Shimazaki et al. (14) showed a relationship between periodontitis and ECG abnormalities and CVD. Additionally, Im et al. (15) concluded that AF patients with periodontitis, as representative of chronic inflammation, were more prone to have arrhythmic events such as AF, atrial flutter, atrial tachycardia, and any other events than those without periodontitis.

Studies have shown that the QT, QTc, QTd, QTdc JT, JTc and Tp-e intervals are a risk predictor for arrhythmia and sudden death (7,8,16-18).

The QT is affected by the QRS duration (19). QTd has been declared as an indicator of ventricular arrhythmias (17). Also, an increase in QTd was found to be related to sudden death (18).

The JT interval is the portion of the QT that only shows repolarisation (20). The Tp-e range is a relatively new electrocardiographic parameter showing the entire repolarisation distribution (21,22).

Besides, rates of Tp-e/QTc (23) and Tp-e/JTc (24) have also been found to be related to malignant ventricular arrhythmias.

Periodontitis has been suggested to cause CVDs in different ways. For whatever reason, our study showed that these patients were prone to malignant ventricular arrhythmias. In addition to conventional risk factors for CVDs, inflammation is also considered as being a probable risk factor for CVDs.

## Conclusion

Our study showed that arrhythmic ECG markers significantly increased in patients with severe periodontitis.

In future extensive prospective studies, we think that these arrhythmic predictors should be evaluated to predict malignant arrhythmias.

Automatic methods are more recommended than manual measurements (25). Besides, the number of patients in this study may be comparatively small.

### Ethics

**Ethics Committee Approval:** The study was conducted after obtaining ethical approval from the Bolu Abant İzzet Baysal University Ethics Committee (decision number: 2019/264, date: 21/11/2019).

**Informed Consent:** All patients agreed to participate in the study and gave their written informed consent.

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## References

1. Johnson L, Bhutani VK. The clinical syndrome of bilirubin-induced neurologic dysfunction. Semin Perinatol 2011; 35: 101-13.
2. Li X, Kolltveit KM, Tronstad L, Olsen I. Systemic diseases caused by oral infection. Clin Microbiol Rev 2000; 13: 547-58.
3. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999; 4: 1-6.
4. Lang NP, Bartold PM. Periodontal health. J Periodontol 2018; 89(Suppl 1): S9-s16.
5. Suzuki JI, Sato H, Kaneko M, Yoshida A, Aoyama N, Akimoto S, et al. Periodontitis and myocardial hypertrophy. Hypertens Res 2017; 40: 324-8.
6. Monitillo F, Leone M, Rizzo C, Passantino A, Iacoviello M. Ventricular repolarization measures for arrhythmic risk stratification. World J Cardiol 2016; 8: 57-73.
7. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. Circulation 2009; 119: 663-70.
8. Antzelevitch C. T peak-Tend interval as an index of transmural dispersion of repolarization. Eur J Clin Invest 2001; 31: 555-7.
9. Bazett HC. An analysis of the time relations of electrocardiograms. Heart 1920; 7: 353-70.
10. Stassen FR, Vainas T, Bruggeman CA. Infection and atherosclerosis. An alternative view on an outdated hypothesis. Pharmacol Rep 2008; 60: 85-92.
11. Chapple ILC, Mealey BL, Van Dyke TE, Bartold PM, Dommisch H, Eickholz P, et al. Periodontal health and gingival diseases and conditions on an intact and a reduced periodontium: Consensus report of workgroup 1 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Clin Periodontol 2018; (89 Suppl 1): S74-S84.
12. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-95.
13. Knutsen R, Knutsen SF, Curb JD, Reed DM, Kautz JA, Yano K. The predictive value of resting electrocardiograms for 12-year incidence of coronary heart disease in the Honolulu Heart Program. J Clin Epidemiol 1988; 41: 293-302.
14. Shimazaki Y, Saito T, Kiyohara Y, Kato I, Kubo M, Iida M, et al. Relationship between electrocardiographic abnormalities and periodontal disease: the Hisayama Study. J Periodontol 2004; 75: 791-7.
15. Im SI, Heo J, Kim BJ, Cho KI, Kim HS, Heo JH, et al. Impact of periodontitis as representative of chronic inflammation on long-term clinical outcomes in patients with atrial fibrillation. Open heart 2018; 5: e000708.
16. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardio 1993; 72: 23b-5b.
17. Macfarlane PW. Measurement of QT dispersion. Heart 1998; 80: 421-3.
18. Zareba W, Moss AJ, le Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. Am J Cardiol 1994; 74: 550-3.
19. Crow RS, Hannan PJ, Folsom AR. Prognostic significance of corrected QT and corrected JT interval for incident coronary heart disease in a general population sample stratified by presence or absence of wide QRS complex: the ARIC Study with 13 years of follow-up. Circulation 2003; 108: 1985-9.
20. Bihlmeyer NA, Brody JA, Smith AV, Warren HR, Lin H, Isaacs A, et al. ExomeChip-Wide Analysis of 95 626 Individuals Identifies 10 Novel Loci Associated With QT and JT Intervals. Circ Genom Precis Med 2018; 11: e001758.
21. Antzelevitch C, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, Shimizu W, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart rhythm 2007; 4: 1114-6; author reply 1116-9.
22. Erikssen G, Liestol K, Gullestad L, Haugaa KH, Bendz B, Amlie JP. The terminal part of the QT interval (T peak to T end): a predictor of mortality after acute myocardial infarction. Ann Noninvasive Electrocardiol 2012; 17: 85-94.
23. Zhao X, Xie Z, Chu Y, Yang L, Xu W, Yang X, et al. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 2012; 35: 559-64.
24. Alvarado-Serrano C, Ramos-Castro J, Pallas-Areny R. Novel indices of ventricular repolarization to screen post myocardial infarction patients. Comput Biol Med 2006; 36: 507-15.
25. Grasser EK, Ernst B, Thurnheer M, Schultes B. QT Interval Shortening After Bariatric Surgery Depends on the Applied Heart Rate Correction Equation. Obes Surg 2017; 27: 973-82.

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# Neurodevelopmental Evaluation of Term Newborns with Significant Hyperbilirubinemia

## Belirgin Hiperbilirubinemili Term Yenidoğanların Nörogelişimlerinin Değerlendirilmesi

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## ABSTRACT

**Introduction:** When bilirubin attains high levels, it can lead to different degrees of brain damage. In this study, we aimed to evaluate the neurodevelopment status of term newborns treated for hyperbilirubinemia in the neonatal period.

**Methods:** The study group consisted of 48 children with total bilirubin >22 mg/dL in the neonatal period. The study group was compared with 50 healthy children determined as the control group. Detailed physical examination of all the children was performed and anthropometric measurements were taken. Previous hospitalisation data of the study group were examined, and the socio-demographic data of the parents were also obtained. All the children underwent neurodevelopmental screening with the Denver II Developmental Screening test (DDST).

**Results:** No statistically significant difference was found between the hyperbilirubinaemia group and control group in terms of the male/female ratio, age, weight, height, body mass index and prophylactic iron use. Maternal and paternal demographic data were compared, and there was no significant difference. The general results of the DDST were compared, and significant neurodevelopmental retardation was found in the study group ($p<0.001$). For both groups, the DDST development areas were compared; language development ($p<0.001$) and fine motor development ($p=0.046$) were delayed in the study group. In the receiver operating characteristic curve analysis, the risk of developmental retardation was found to be higher in newborns with bilirubin values greater than 23.5 mg/dL ($p=0.009$).

**Conclusion:** Significant hyperbilirubinaemia is an important risk factor for the retarded child development. Therefore, developmental screening tests should be performed at regular intervals for the early detection of developmental delays and to start the appropriate treatment.

**Keywords:** Neonatal jaundice, hyperbilirubinemia, neurodevelopment, language development, Denver II

## ÖZ

**Amaç:** Bilirubin yüksek seviyelere ulaştığında farklı derecelerde beyin hasarına yol açabilir. Bu çalışmada yenidoğan döneminde hiperbilirubinemi nedeni ile tedavi edilmiş term bebeklerin nörogelişim durumları değerlendirildi.

**Yöntemler:** Çalışma grubu olarak yenidoğan döneminde total bilirubini 22 mg/dL'nin üzerinde olan ve term olarak doğmuş 48 çocuk ve kontrol grubu olarak 50 sağlıklı çocuk karşılaştırıldı. Tüm çocıkların ayrıntılı fizik muayenesi yapıldı ve antropometrik ölçümleri alındı. Çalışma grubuna ait eski yatış verileri incelendi. Anne ve babaya ait sosyo-demografik veriler sorgulandı. Tüm çocuklara Denver II Gelişimsel Tarama testi yapıldı (DGTT).

**Bulgular:** Hiperbilirubinemi grubu ve kontrol grubu arasında erkek/kız oranı, yaş, ağırlık, boy, vücut kitle indeksi, profilaktik demir kullanımı açısından istatistiksel olarak fark bulunmadı. Maternal ve paternal demografik veriler karşılaştırıldığında anlamlı fark yoktu. DGTT genel sonuçları karşılaştırıldığında, çalışma grubunda belirgin nörogelişim geriliği saptandı ($p<0,001$). Her iki grup DGTT gelişim alanları karşılaştırıldığında çalışma grubunda dil ($p<0,001$) ve ince motor ($p=0,046$) gelişimi geri bulundu. Yapılan receiver operating characteristic curve analizinde 23,5 mg/dL üzerindeki bilirubin değerlerine sahip olan yenidoğanlarda gelişim geriliği görülme riski daha fazla bulundu ($p=0,009$).

**Sonuç:** Belirgin hiperbilirubinemi çocuğun gelişimi açısından önemli bir risk faktörüdür. Bu nedenle gelişimsel gecikmenin erken tespiti ve uygun tedaviye başlanması için gelişimsel tarama testleri düzenli aralıklarla yapılmalıdır.

**Anahtar Kelimeler:** Yenidoğan sarılığı, hiperbilirubinemi, nörogelişim, dil gelişimi, Denver II

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## Introduction

In the first week of life, high bilirubin level is an important indicator because free bilirubin can cross the blood brain barrier. It is well known that bilirubin causes serious brain damage when it attains very high levels. Damage to the central nervous system varies depending on the bilirubin level. This neurological effect has a broad spectrum, from mild impacts such as isolated auditory neuropathy, movement disorders, dystonia, cognitive disorders, mild mental retardation to much more severe impacts such as severe neuromotor deficits due to acute bilirubin encephalopathy and auditory sequelae (1-3).

Today, most patients with high bilirubin levels do not experience neurological damage due to the modern treatment methods and because patients can benefit more from medical services (4,5). However, there are few patients who still develop mild neurological damage, and detecting these patients is critical. Essentially, the population in which we can make a difference is among patients with little damage. Therefore, in addition to the hearing assessment, which is usually what we pay the most attention to during follow-up, neurodevelopmental screening tests should be carried out diligently (6-8).

In our study, we made a neurodevelopmental evaluation of newborns with different bilirubin levels. We used the Denver II Developmental Screening test (DDST), which included personal-social, fine motor, language and gross motor assessments.

## Methods

This prospective and comparative study was approved by the local ethics committee (approval number: GOKAEK/2017-550, date: 08.02.2017). All the participants were informed verbally and in writing about the study and their written consents were obtained.

### Study Groups

The study included two groups: study group and control group. The study group consisted of 48 cases who were treated for a high bilirubin (total bilirubin) level (>22 mg/dL) and were born at 38 to 42 gestational weeks. Seventy-seven patients who were treated in our neonatal intensive care unit due to hyperbilirubinemia between 2015 and 2016 (>22 mg/dL) were identified. Those who were reachable by phone were included in the study. The control group consisted of 50 healthy children who visited our outpatient clinic. Exclusion criteria included preterm births (<38 weeks), hypoxic delivery, intrauterine growth retardation, major congenital malformation, hospitalisation for any reason, hearing problems, any chronic disease and maternal disease during pregnancy.

Detailed physical examinations and neurological examinations of the children were performed. Weight, height and body mass index (BMI) of all the cases were recorded. Mothers were asked if they gave their children iron prophylaxis between 4 and 12 months. Children's Hearing tests (Brain stem evoked response audiometry - BERA) were performed. The hospitalisation files of the children in the study group were examined and the data were recorded. Socio-demographic data of the parents was also obtained.

### Neurodevelopmental Assessment

DDST was used in the neurodevelopmental evaluation of the patients. The same paediatrician who had the certificate evaluated all the children. Denver developmental screening test, which was defined by Frankenburg and Dodds in 1967, was revised in 1990 as Denver II. In our study, we used the version of this test standardised by Yalaz et al. (9) in 2009.

DDST is applied to 0-6 years old children with a healthy appearance. It consists of 134 items created to evaluate the ability in 4 developmental areas according to age: personal-social (21 items), fine motor (33 items), language (42 items) and gross motor (38 items). The test results in 4 possible evaluations: normal, abnormal, suspicious and non-testable.

### Statistical Analysis

The Shapiro-Wilk test was used to perform normality control on the histogram, Q-Q plot and box plot charts. Data were expressed as median, minimum, maximum, frequency and percentage. The measurement variables between the two groups were analysed with the Mann-Whitney U test. Receiver operating characteristic (ROC) analysis was performed. Diagnostic tests (sens., Spe., PPV, NPV, Accuracy) and 95% confidence intervals were given. Nominal variables were evaluated with Yates corrected chi square test with Yates correction and Fisher's exact probability tests. Odds ratio values and 95% confidence intervals were calculated. The limit of significance was taken as $p<0.05$ and bidirectional. The analyses were performed using NCSS 10 (2015. Kaysville, Utah, USA) software program.

## Results

This study included 48 newborns with hyperbilirubinaemia and 50 healthy children. There was no significant difference between the hyperbilirubinaemia and control groups in terms of the female/male ratio ($p=0.54$). The average age in the study group was 37.3±8.3 months, the average weight was 14.8±2.6 kg, the average height was 100.2±7.2 cm, and the average BMI was 14.8±1.1. The mean age in the control group was 41.7±10.2 months, the average weight was 14.6±2.2 kg, the average height was 101.8±6.8 cm, and the average BMI was 14.1±1.1. In terms of age, weight, height and BMI, no significant difference was found between the study and control groups ($p=0.14$), ($p=0.66$), ($p=0.42$) and ($p=0.13$), respectively. There was no difference between the use of iron prophylaxis in both groups ($p=0.85$) (Table 1).

Hospital records of the children in the hyperbilirubinaemia group were examined. The average gestational age was 38.7±0.4 weeks, mean birth weight was 3185±335 g and the duration of hospitalisation was 3.22±1.4 days. The time of admission was found to be 4.3±2.4 days after birth. The cause of hyperbilirubinaemia was ABO incompatibility in 17 patients, Rh incompatibility in 4 patients, G6PDH deficiency in 5 patients and weight loss in 3 patients. The cause of the hyperbilirubinaemia was not found in 19 patients. Blood exchange was performed in 2 patients, IVIG treatment was applied to 9 patients, and phototherapy was given to all the patients.

The maternal and paternal demographic data of the study and control groups were compared. No statistically significant difference was found

between the two groups in terms of maternal and paternal age and education level, number of children in the family and monthly income (Table 2).

DDST general results were evaluated. There was a statistically significant difference between the two groups in terms of neurodevelopment. Neurodevelopment was significantly lower in the hyperbilirubinaemia group (p<0.001) (Table 3).

DDST results were evaluated according to developmental areas. There was no statistical difference in the personal-social (p=0.26) and gross motor (p=0.31) areas in both groups. In the hyperbilirubinaemia group, the developmental delay was statistically significant in the language and fine motor areas (p<0.001), (p=0.046) respectively (Table 4).

ROC curve analysis was performed to determine the cut-off value of total bilirubin in predicting developmental delay. Total bilirubin cut-off value was found to be 23.5 mg/dL (p=0.009) (Figure1).

## Discussion

Hyperbilirubinaemia, one of the most common problems of the neonatal period, is critical because it affects brain development when the bilirubin level exceeds a certain threshold value.

Bilirubin toxicity has been associated with many conditions such as neurodevelopmental delays, cognition-speech-language development, attention deficit-hyperactivity disorder and autism (6-10).

**Table 1. The clinical characteristics of the study and control groups of patients**

| Characteristics | Study group (n=48) % | Control group (n=50) % | p |
|---|---|---|---|
| Gender (male/female) | (26) 54/(22) 46 | (23) 48/(27) 54 | 0.54 |
| Age (months) | 37.3±8.3 | 41.7±10.2 | |
| Mean ± SD | (24-58) | (25-62) | 0.14 |
| Height (cm) | 100.2±7.2 | 101.8±6.8 | 0.42 |
| Mean ± SD | (83-120) | (91-120) | |
| Weight (kg) | 14.8±2.6 | 14.6±2.2 | 0.66 |
| Mean ± SD | (9-25) | (11.8-23.7) | |
| BMI | 14.8±1.1 | 14.1±1.1 | 0.13 |
| Mean ± SD | (12.6-17.4) | (11.8-17.0) | |
| Iron intake, n (%) | | | 0.85 |
| None | (9) 18.8 | (8) 16 | |
| Regular | (28) 58.3 | (32) 64 | |
| Irregular | (11) 22.9 | (10) 20 | |

SD: Standard deviation, BMI: body mass index, statistically significant increased values (p<0.05), n: number of patients

We evaluated babies with hyperbilirubinaemia using the DDST. In our study, when we compared the patients with hyperbilirubinemia with the control group, we found that their neurodevelopment was significantly retarded (p<0.001). The literature suggests that there is a significant relationship between neonatal hyperbilirubinemia and neurodevelopmental delay, but this relationship seems quite complicated. In a recent study, the factors affecting neurodevelopmental delay in preterm and term babies were examined. In preterm infants, the most important risk factors were intensive care period, ototoxic drug use, mechanical ventilation and hyperbilirubinemia, while in term

**Table 2. Maternal and paternal demographic characteristics**

| Characteristics | Study group (n=48) % | Control group (n=50) % | p |
|---|---|---|---|
| Maternal age | 28.6±6.8 | 28.9±5.3 | 0.57 |
| Mean ± SD | (17-46) | (19-40) | |
| Maternal education | | | 0.33 |
| Illiterate | (3) 6 | (0) 0 | |
| Primary school | (28) 58 | (33) 66 | |
| Secondary school | (8) 17 | (6) 12 | |
| High school | (6) 13 | (9) 18 | |
| University | (3) 6 | (2) 4 | |
| Paternal age | 31.7±7.13 | 34.3±7.5 | 0.16 |
| Mean ± SD | (20-53) | (19-53) | |
| Paternal education | | | 0.35 |
| Illiterate | (2) 4 | (0) 0 | |
| Primary school | (23) 48 | (25) 50 | |
| Secondary school | (13) 27 | (9) 18 | |
| High school | (8) 17 | (11) 22 | |
| University | (2) 4 | (5) 10 | |
| Number of children | | | 0.10 |
| 1 | (20) 42 | (10) 20 | |
| 2 | (10) 21 | (22) 44 | |
| 3 | (10) 21 | (11) 22 | |
| 4 | (6) 12 | (5) 10 | |
| 5 | (2) 4 | (2) 4 | |
| Monthly income (Turkish Liras) | | | 0.96 |
| <2000 | (12) 25 | (12) 24 | |
| 2000-5000 | (32) 67 | (33) 66 | |
| >5000 | (4) 8 | (5) 10 | |

SD: Standard deviation, statistically significant increased values (p<0.05), n: number of the patients

**Table 3. Denver II developmental screening test general results**

| Results | Study group n= 48 (%) | Control group n= 50 (%) | OR (95% CI) | p |
|---|---|---|---|---|
| Normal | 21 (44) | 43 (86) | 7.89 (2.9-21.1) | <0.001 |
| Suspicious | 16 (33) | 5 (10) | | |
| Abnormal | 11 (23) | 2 (4) | | |
| Non-testable | 0 (0) | 0 (0) | | |

Statistically significant increased values (p<0.05), OR: odds ratio, CI: confidence interval, n: number of patients

**Table 4. Denver II developmental screening test results according to the developmental areas**

| Developmental areas | Study group (n) | | Control group (n) | | OR (95% CI) | p |
|---|---|---|---|---|---|---|
| | Suspicious | Abnormal | Suspicious | Abnormal | | |
| Personal-social | 1 | 3 | - | 2 | - | 0.26 |
| Fine motor | 4 | 3 | 1 | - | 5.51 (1.1-27.1) | 0.046 |
| Language | 13 | 12 | 2 | 1 | 14.4 (3.9-52.7) | <0.001 |
| Gross motor | 2 | 4 | 3 | - | - | 0.31 |

Statistically significant increased values (p<0.05), OR: odds ratio, CI: confidence interval

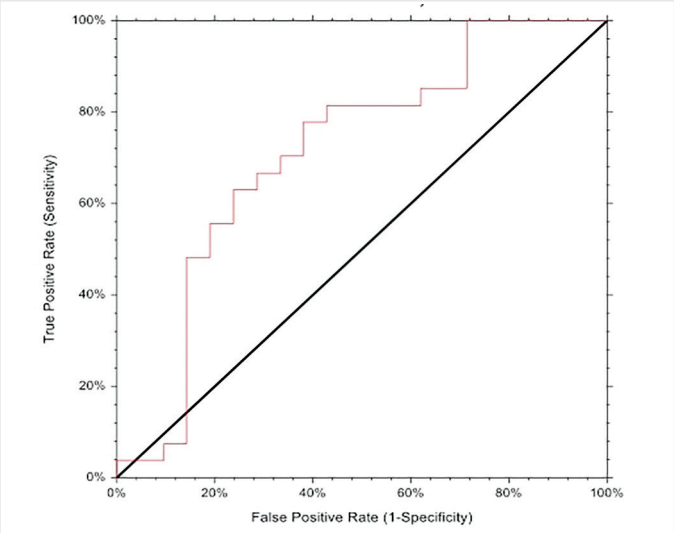


**Figure 1.** ROC curve analysis; serum total bilirubin cut-off value to predict developmental delay (p=0.009), (Empirical estimate of AUC: 0.711, AUC's SD: 0.081, Lower 95% CI: 0.515, Upper 95% CI: 0.836)

ROC: Receiver operating characteristic, AUC: area under curve, CI: confidence interval, SD: standard deviation

infants, the risk factors were hyperbilirubinemia and Apgar score (11,12). Another study in term babies found that the higher the bilirubin level, the more negatively the development was affected (13).

Preterm infants are more sensitive to hyperbilirubinaemia. Therefore, the relationship between hyperbilirubinaemia and developmental retardation has been studied mostly in preterm infants. In the many studies conducted in this group, the effect of hyperbilirubinaemia on developmental delay has been found to be quite pronounced (14-17).

As the bilirubin level in the blood increases, newborns are more affected by its possible toxic effects. In our study, newborns with a total bilirubin level greater than 23.5 mg/dL were found to be more at risk in terms of neurodevelopmental delay. In a study with the Baroda developmental screening test, they found that neurodevelopment delay was more likely in term babies with a total bilirubin level greater than 22 mg/dL (13).

DDST is a very reliable and widely used test in evaluating the neurodevelopment of children aged 0-6 years. It has been used to evaluate neurodevelopment in different case groups such as adenotonsillar hypertrophy, congenital heart disease and babies from pre-eclamptic mothers (18-20).

In our study, there was a marked delay in language development in the hyperbilirubinaemia group (p<0.001). In many studies, the effect of hyperbilirubinemia on neurodevelopment has been investigated, but only the impact on hearing has been revealed. None of these studies focused on the relationship between speech delay and hyperbilirubinaemia. There is limited information in the literature about the effect of hyperbilirubinaemia on hearing and language development (18,19,21).

In our study, a statistically significant fine motor developmental delay was found in the hyperbilirubinaemia group compared to the control group (p<0.046). The link between motor retardation and dyskinetic cerebral palsy is well known in newborns exposed to high bilirubin toxicity. However, the effect of exposure to low-moderate bilirubin levels on motor development is not fully understood. More research is needed to understand motor disorders that can be caused by neonatal hyperbilirubinaemia. Movement disorders and cerebral palsy may also develop in preterm babies exposed to low-to-moderate bilirubin levels (22,23).

There was no significant difference in personal-social and gross motor development between the two groups in our study.

Factors such as the paternal and maternal level of education level and the income level of the family can play an important role in the child's development. In a large-scale study, maternal education has been shown to have a significant effect on the language and fine motor development of preschool children. It was also found that the mother was more effective than the father in impacting the development of the child in early childhood (24-26). In our study, no difference was found between the two groups in terms of the level of education of the parents, the income level of the family and the number of children in the family.

The fact that our study was conducted with a small number of cases can be considered as a limitation. However, the exclusion criteria have been expanded to obtain more accurate results. It is also an advantage that the same person evaluated all children, and the study was done prospectively.

## Conclusion

In children without significant developmental disorders, cases of mild neurological damage may not be detected by normal physical examination. In children treated for significant hyperbilirubinaemia, developmental screening tests should be performed at regular intervals, in addition to the detailed systemic examination and hearing testing. Early detection of developmental delays in children is essential for initiating the right treatment in a timely manner.

**Ethics**

**Ethics Committee Approval:** This prospective and comparative study was approved by the local ethics committee (approval number: GOKAEK/2017-550, date: 08.02.2017).

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

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

**Authorship Contributions:** Concept - G.Ö., S.C.; Design - G.Ö., S.C.; Data Collection or Processing - G.Ö.; Analysis or Interpretation - G.Ö., S.C.; Literature Search - G.Ö.; Writing - G.Ö.

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

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## References

1. Johnson L, Brown AK, Bhutani VK. BIND-a clinical score for bilirubin induced neurologic dysfunction in newborns. Pediatrics Suppl 1999; 104: 746-7.
2. Shapiro SM. De nition of the clinical spectrum of kernicterus and bilirubin induced neurologic dysfunction (BIND). J Perinatol 2005; 25: 54-9.
3. Shapiro SM. Kernicterus. In: Stevenson DK, Maisels MJ, Watchko JF, eds. Care of jaundiced neonate. New York: McGraw-Hill 2012: 229- 42.
4. Stevenson DK, Fanarof AA, Maisels MJ, Young BW, Wong RJ, Vreman HJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics 2001; 108: 31-9.
5. American Academy of Pediatrics, Provisional Committee for Quality Improvement. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. Pediatrics 1994; 94: 558-65.
6. Volpe JJ. Neurology of the Newborn, 4th Edition. Philadephia: WB Saunders; 2001.
7. Bhutani VK, Johnson LH, Maisels JM, Newman TB, Phibbs C, Stark AR, et al. Kernicterus: Epidemiological strategies for its prevention through systems-based approaches. J Perinatol 2004; 24: 650-62.
8. L. Wusthoff CJ, Loe IM. Impact of bilirubin-induced neurologic dysfunction on neurodevelopmental outcomes. Semin Fetal Neonatal Med 2015; 20: 52-7.
9. Yalaz K, Anlar B, Bayoğlu BU. Denver II gelişimsel tarama testi türkiye standardizasyonu. Gelişimsel çocuk nörolojisi derneği; 2009.
10. Maimburg RD, Bech BH, Vaeth M, Moller-Madsen B, Olsen J. Neonatal jaundice, autism, and other disorders of psychological development. Pediatrics 2010; 126: 872-8.
11. Watchko JF, Tribelli C. Bilirubin-induced neurologic damage- mechanisms and management approaches. N Engl J Med 2013; 369: 2021-30.
12. Nascimento GB, Kessler TM, Ramos de Souza AP, Costa I, Moraes AB. Risk indicators for hearing loss and language acquisition and their relationship with socioeconomic, demographic and obstetric variables in preterm and term babies. Codas 2020; 32: e20180278.
13. Thirunavukkarasu AB, Vishnu BB, Noyal MJ. Association between peak serum bilirubin and neurodevelopmental outcomes in term babies with hyperbilirubinemia. Indian J Pediatr 2012; 79: 202-6.
14. Amin SB. Clinical assessment of bilirubin-induced neurotoxicity in premature infants. Semin Perinatol 2004; 28: 340-7.
15. Oh W, Tyson JE, Fanaroff AA, Vohr BR, Perritt R, Stoll BJ, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003; 112: 773-9.
16. Graziani LJ, Mitchell DG, Kornhauser M, Pidcock FS, Merton DA, Stanley C, et al. Neurodevelopment of preterm infants: neonatal neurosonographic and serum bilirubin studies. Pediatrics 1992; 89: 229-34.
17. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000 g: 1992–1995. Arch Pediatr Adolesc Med 2000; 154: 725-31.
18. Ozmen A, Terlemez S, Tunaoglu FS, Soysal S, Pektas A, Cilsal E, et al. Evaluation of Neurodevelopment and Factors Affecting it in Children with Acyanotic Congenital Cardiac Disease. Iran J Pediatr 2016; 26: e3278.
19. Soylu E, Soylu N, Polat C, Sakallıoğlu O, Uçur, O, Bozdoğan G. Developmental delays in preschool children with adenotonsillar hypertrophy. Kulak Burun Bogaz Ihtis Derg 2016; 26:129-34.
20. Ertekin AA, Kapudere B, Eken MK, Ilhan G, Dırman S, Sargın MA, et al. Does aggressive and expectant management of severe preeclampsia affect the neurologic development of the infant? Int J Clin Exp Med 2015; 8: 19325-31.
21. Amin SB, Prinzing D, Myers G. Hyperbilirubinemia and Language Delay in Premature Infants. Pediatrics 2009; 123: 327-31.
22. Rose J, Vassar R. Movement Disorders Due to Bilirubin Toxicity. Semin Fetal Neonatal Med 2015; 20: 20-5.
23. Przekop A, Sanger TD. Birth-related Syndromes of Athetosis and Kernicterus. Handb Clin Neurol 2011; 100: 387-95.
24. Durmazlar N, Ozturk C, Ural B, Karaagaoglu E, Anlar B. Turkish children's performance on Denver II: Effect of sex and mother's education. Dev Med Child Neurol 1998; 40: 411-6.
25. Rowe ML, Raudenbush SW, Goldin-Meadow S. The pace of vocabular growth helps predict later vocabulary skill. Child Dev 2012; 83: 508-25.
26. Gonzalez JE, Acosta S, Davis H, Pollard-Durodola S, Saenz L, Soares D, et al. Latino maternal literacy beliefs and practices mediating socioeconomic status and maternal education effects in predicting child receptive vocabulary. Early Educ Dev 2017; 28: 78-95.

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# Non-operating Room Anaesthesia Practices in an Endoscopy Unit at a Tertiary Centre: A Retrospective Evaluation

## Tersiyer Bir Merkezde Endoskopi Ünitesinde Ameliyathane Dışı Anestezi Uygulamaları: Retrospektif Değerlendirme

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## ABSTRACT

**Introduction:** In recent years, gastrointestinal endoscopic procedures have been performed with sedo-analgesia at many centres. We aimed to present a 1-year retrospective analysis of non-operating room anaesthesia (NORA) applications at the endoscopy unit of our research and training hospital.

**Methods:** We retrospectively analysed the NORA applications at our endoscopy unit between 01.01.2018 and 31.12.2018. The gender, age, American Society of Anaesthesiologist (ASA) score, intervention, anaesthesia drugs and complications were retrospectively analysed for 18.291 patients.

**Results:** The sample comprised 47.03% men (n=8,602) and 52,97% women (n=9,689), with a mean age of 58.75±13.75 years (range, 16-92 years). Per the ASA classification, there were 57.22% (n=10,467), 37.92% (n=6,936), 4.79% (n=876) and 0.07% (n=12) patients with ASA grades I, II, III and IV, respectively. Gastroscopy (n=9,481, 51.84%), followed by colonoscopy (n=5,596, 30.60%) were the most commonly performed procedures. The combination of midazolam and meperidine; propofol, midazolam and meperidine and midazolam alone were administered for 43.99% (n=8,046); 53.48% (n=9,782) and 2.54% (n=463) of the patients, respectively. In a patient with hypertension, no major complication was encountered except for pneumothorax during the endoscopic retrograde cholangiopancreatography. The most common significant complication was desaturation; seen in 3.05% of the patients (n=559).

**Conclusion:** Endoscopy units are non-operating units, albeit with a high patient volume. Thus, adopting sedation for interventional procedures in these units simplifies the procedure and increases patient safety and satisfaction, along with physician's comfort. Compared with the studies performed at our clinic, we found similar complication rates as with sedo-analgesia protocols.

**Keywords:** Endoscopy unit, non-operating room anaesthesia applications, sedation

## ÖZ

**Amaç:** Son yıllarda birçok merkezde gastrointestinal sistem endoskopik işlemleri sedo-analjezi ile yapılmaktadır. Çalışmamızda bir eğitim ve araştırma hastanesinin endoskopi ünitesinde bir yıllık süreçte ameliyathane dışı anestezi (ADA) uygulamalarına ait deneyimlerimizin retrospektif analizlerini sunmayı amaçladık.

**Yöntemler:** 01.01.2018 ve 31.12.2018 tarihleri arasında endoskopi ünitesindeki ADA uygulamalarımızı geriye dönük araştırdık. ADA uyguladığımız 18.291 hastanın cinsiyetleri, yaşları, American Society of Anesthesiologist (ASA) skorları, yapılan girişimleri, uygulanan anestezi ilaçları ve komplikasyonları hasta dosyalarından geriye dönük incelendi.

**Bulgular:** Olguların cinsiyet dağılımı erkek/kadın 8.602 (%47,03)/9.689 (%52,97), yaş ortalamaları 58,75±13,75 yıl, yaş dağılımı 16-92 yaş arasındaydı. ASA sınıflaması ASA I 10.467 (%57,22), ASA II 6.936 (%37,92), ASA III 876 (%4,79), ASA IV 12 (%0,07) hasta şeklindeydi. En sık 9481 (%51,84) olguyla gastroskopi işlemi yapılmış olup bunu 5.596 (%30,60) olgu ile kolonoskopi işleminin takip ettiği görüldü. Olguların 8.046'sına (%43,99) midazolam + meperidin kombinasyonu, 9.782'sine (%53,48) propofol + midazolam + meperidin kombinasyonu ve 463'üne (%2,53) sadece midazolam sedasyonu uygulandığı tespit edildi. Hipertansiyonu olan bir hastada endoskopik retrograd kolanjiyopankreatografi işlemi sırasında pnömotoraks gelişmesi dışında major bir komplikasyonla karşılaşılmadı. Minör komplikasyonlardan en sık 559 (%3,05) olgu ile desatürasyon görüldüğü tespit edildi.

**Sonuç:** Endoskopi üniteleri sirkülasyonun hızlı olduğu ameliyathane dışı ünitelerdir. Bu ünitelerde girişimsel işlemler sırasında hastalara verilen sedasyon; işlemi kolaylaştırmakta, hem hasta güvenliğini ve memnuniyetini hem de hekim konforunu artırmaktadır. Kliniğimizde kullanılan sedo-analjezi protokollerinin yapılan çalışmalarla karşılaştırıldığında komplikasyon oranlarının benzer olduğunu gördük.

**Anahtar Kelimeler:** Endoskopi ünitesi, ameliyathane dışı anestezi uygulamaları, sedasyon

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## Introduction

Along with the technological development, nowadays, interventional operations performed for diagnosis and treatment in endoscopy units have increased. Although the appropriate equipment and sufficient number of personnel are available in endoscopy units, which are frequently located outside the operating room, potential complications should always be considered. Non-operating room anesthesia (NORA) applications during the interventional procedures performed in these units; with sedation/analgesia techniques, it is important in terms of both patient comfort and safety and surgeon comfort by increasing the success of the procedure applied to the inactive patient (1).

Gastroscopy, colonoscopy, endoscopic retrograde cholangiopancreatography (ERCP), rectosigmoidoscopy, colon polypectomy, balloon dilatation, stent placement in strictures, percutaneous endoscopic gastrostomy (PEG), endoscopic mucosal resection (EMR), endoscopic ultrasound (EUS) and endoscopic rectal ultrasound (ERUS) are some of the procedures performed in endoscopy units.

In recent years, performing endoscopy procedures with anesthesia is preferred because of the priority of patient comfort and satisfaction and increasing the quality of the procedure (2). Demand for anesthesia in endoscopic procedures has increased (3). In our clinic, endoscopy procedures are performed under anesthesia except for contraindications and the patient refuse anesthesia. Anesthesiologist and anesthesia technician perform the anesthesia procedures.

In our study, we aimed to present our experience by retrospectively evaluating the demographic data of the patients who underwent diagnostic or therapeutic gastrointestinal endoscopic procedures between 01.01.2018 and 31.12.2018, the interventional procedures, anesthesia agents used and anesthesia complications.

## Methods

After obtaining the approval of the Ethics Committee of University of Health Science Turkey, İstanbul Training and Research Hospital, dated 12.04.2019 with approval number of 1796, 18,500 interventional procedures performed with anesthesia in the endoscopy unit for one year between 01.01.2018 and 31.12.2018 were evaluated. Patient information was scanned retrospectively from the anesthesia files; therefore, written consent could not be obtained from the patients for our study. Patients' gender, age, American Society of Anaesthesiologist (ASA) scores, interventional procedures, sedation agents used, major and minor complications were analyzed. Two hundred nine patient files were excluded due to lack of data. Data of 18,291 patients were included in the study.

Our NORA equipment has been determined according to the NORA practices guide published by Turkish Society of Anesthesiology and Reanimation in 2015. In the endoscopy unit, which has five operation rooms, each room has an oxygen source, an aspirator, a laryngoscope, an ambu and a monitor that measures heart rate, arterial blood pressure and saturation. In addition, there is an emergency cabinet containing emergency resuscitation materials, a defibrillator and an anesthesia device in the unit. Each patient is examined preoperatively before the procedure and then an appropriate sedation method is planned. The sedation process is initiated after monitoring the patients whose written consent had taken, opening the arteries and administered 100% oxygen with the mask. In our clinic, which has a recovery room, patients are followed up using the Aldrete scoring (Table 1) after the procedure, and patients with a score of 9 and above are discharged with recommendations.

In our study, if the heart rate decreased 25% below normal and was treated with atropine, it was evaluated as bradycardia. Those whose spontaneous breathing fell below 12 per minute were recorded as respiratory depression. A decrease in oxygen saturation below 90% in the fingertip probe was accepted as desaturation. Patients with respiratory depression and desaturation were treated with maneuvers that stimulate breathing, changing the position of the head, using an airway, and oxygen support with a mask. Those whose recovery time exceeded 10 minutes were recorded as prolonged recovery time.

### Statistical Analysis

The data were evaluated by the researchers using the Statistical Package for Social Sciences (SPSS) for Windows 21.0 statistical package program in computer environment. Descriptive statistics of numerical variables were given as mean ± standard deviation, while categorical variables were expressed as frequency (n) and percentage (%).

## Results

The information of 209 out of the 18,500 patients who were examined retrospectively from the patient files could not be reached due to the lack of registration. 18,291 cases were included in the study. The gender distribution of 18,291 patients was found as male/female 8,602/9,689. The age distribution of the cases was between 16 and 92 years while the

**Table 1. Aldrete scoring**

| | | Score |
|---|---|---|
| **Activity** | Can move all four extremities | 2 |
| | Can move two extremities | 1 |
| | Cannot move extremities voluntarily or by order | 0 |
| **Respiration** | Can breathe and cough | 2 |
| | Dysdpneic or restricted breathing | 1 |
| | Apneic | 0 |
| **Circulation** | Blood pressure ±20% of the value before anesthesia | 2 |
| | Blood pressure ±21-49% of the value before anesthesia | 1 |
| | Blood pressure ±50% of the value before anesthesia | 0 |
| **Consciousness** | Fully awake | 2 |
| | Wakes up with calling | 1 |
| | No response | 0 |
| **Oxygen saturation** | Saturation at room air >92% | 2 |
| | $O_2$ is required to keep saturation >92% | 1 |
| | <90% saturation with oxygen application | 0 |

mean age was 58.75±13.75. ASA classification was ASA I 10,467 patients, ASA II 6.936 patients, ASA III 876 patients, ASA IV 12 patients (Table 2).

When the interventional procedures performed are examined; it was observed that 9.481 patients had gastroscopy, 5.596 patients had colonoscopy, 1,239 patients had ERCP, 260 patients rectosigmoidoscopy, 494 patients polypectomy, 104 patients balloon dilatation, 52 patients stent placement, 169 patients PEG procedure, 70 patients EMR, 385 patients EUS, 441 patients ERUS (Table 3, Graphic 1).

**Table 2. Demographic data and ASA scores of the patients**

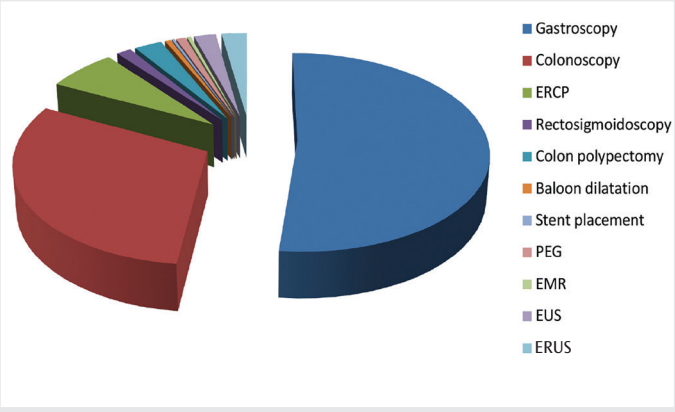
| | Number n (%) |
|---|---|
| Gender (F/M) | 9689 (52.97%) / 8602 (47.03%) |
| ASA I | 10.467 (57.22%) |
| ASA II | 6,936 (37.92%) |
| ASA III | 876 (4.79%) |
| ASA IV | 12 (0.07%) |

F/M: Female/Male, ASA: American Society of Anaesthesiologist

**Table 3. Distribution of interventional operations**

| Interventional operations | Total number of patients n (%) |
|---|---|
| Gastroscopy | 9,481 (51.84%) |
| Colonoscopy | 5,596 (30.60%) |
| ERCP | 1,239 (6.77%) |
| Rectosigmoidoscopy | 260 (1.42%) |
| Colon polypectomy | 494 (2.70%) |
| Baloon dilatation | 104 (0.57%) |
| Stent placement | 52 (0.28%) |
| PEG | 169 (0.92%) |
| EMR | 70 (0.38%) |
| EUS | 385 (2.11%) |
| ERUS | 441 (2.41%) |

ERCP: Endoscopic retrograde cholangiopancreatography, PEG: percutaneous endoscopic gastrostomy, EMR: endoscopic mucosal resection, EUS: endoscopic ultrasound, ERUS: endoscopic rectal ultrasound




**Graphic 1.** Distribution of interventional operations

ERCP: Endoscopic retrograde cholangiopancreatography, PEG: percutaneous endoscopic gastrostomy, EMR: endoscopic mucosal resection, EUS: endoscopic ultrasound, ERUS: endoscopic rectal ultrasound

When the anesthetic agents used in NORA applications were examined, it was seen that 8.046 were given a combination of midazolam + meperidine, 9,782 were given a combination of propofol + midazolam + meperidine, and 463 were given only midazolam (Table 4, Graphic 2).

When complications related to anesthesia were investigated during the procedures, no major complication was encountered except a patient with hypertension developed pneumothorax during the ERCP procedure. It was observed that 33 patients had respiratory depression, 47 patients had bradycardia, 559 patients had desaturation and 84 patients had delay in recovery time (Table 5).

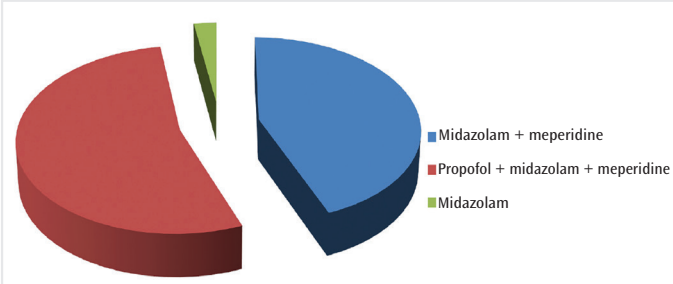
## Discussion

Endoscopy units are among the units where NORA is applied. NORA applications are special because they are far from the operating room and often with limited equipment, and they contain unique physical and clinical differences (1). In our study, it was observed that a total of 18,291 patients were given anesthesia at the endoscopy unit in one year.

All procedures to be performed for a patient preparing for general anesthesia also apply to patients who will undergo NORA. Karamnov et al. (4) reported that insufficient preoperative evaluation was responsible for more than 5% of patients who developed complications in NORA applications. Many studies have shown that a sufficient preoperative evaluation process reduces potential complications and the length of hospitalization (5,6). In our clinic, patients are evaluated preoperatively before the procedure and are processed after necessary consultations.

**Table 4. Distribution of sedative agents used**

| Sedative used | Number n (%) |
|---|---|
| Midazolam + meperidine | 8,046 (43.99 % ) |
| Propofol + midazolam + meperidine | 9,782 (53.48 %) |
| Midazolam | 463 (2.53 %) |




**Graphic 2.** Distribution of sedative agents used

**Table 5. Distribution of complications**

| Complication | Number of patients n (%) |
|---|---|
| Pneumothorax | 1 (0.05%) |
| Respiratory depression | 33 (0.18%) |
| Bradycardia | 47 (3.05%) |
| Desaturation | 559 (3.05%) |
| Prolonged recovery time | 84 (0.25%) |

In the preoperative evaluation of the patients, age and gender factors are first evaluated. Although age alone is not generally significant, it is taken into account in the selection of anesthesia method and depth. However, the rate of comorbidities that increase with age is of great importance (7,8). In our study, it was observed that the mean age of the patients was 58.75±13.75 and the female gender population was higher than that of men. ASA scoring is one of the important steps in terms of determining the risks that may develop during the procedure in advance and being prepared and informing the patient and/or patient relatives. Since comorbid diseases may increase with the increasing age, the ASA risk class may naturally increase (9). In our study, it was seen that there were ASA I 10,467 patients, ASA II 6,936 patients, ASA III 876 patients, and ASA IV 12 patients. The low mean age of the patients was associated with the high number of ASA I and II patients.

The preferred anesthetic agent and anesthesia method for the procedure differ between clinics. Anesthesia method varies depending on the duration of the procedure, degree of pain and complications. The patient's position, anxiety and stress rate, past experiences, allergy history and aspiration risk also play a determining role in the anesthesia method. Anesthetic drugs should be preferred considering the patient's condition, comorbidities and the effects of the drug on hemodynamic parameters (1). Conscious sedation method, in which the patient's spontaneous breathing continues, protective reflexes are maintained, and the desired response is obtained, is a common method. While mild sedation is preferred in the gastroscopy procedure, deeper sedation may be needed in other procedures. Deep sedation or general anesthesia is required in procedures such as EUS, which require the patient to stay still for a long time (10,11). In our study, it was found that the preference for anesthesia was conscious sedation in gastroscopy cases, deep sedation was performed in procedures such as EUS, ERUS and ERCP, and general anesthesia was not needed in any of the cases.

The most commonly used agents in sedo-analgesia applications are propofol, ketamine, midazolam, dexmetomidine, fentanyl, meperidine and morphine (11). Midazolam, which has an amnesic effect, is the most commonly used sedative agent and is generally used in combination with propofol (12). Propofol, on the other hand, is preferred as a sedative due to its rapid recovery and antiemetic properties, but it is preferred to be used with other drugs because it does not have an analgesic effect and may cause complications such as loss of airway reflex, hypotension and bradycardia due to high dose use (13). There are studies reporting that the combined use of propofol and opioids reduces the incidence of nausea, vomiting and respiratory depression, which are side effects related to the use of high doses of opioids (14-17). According to meta-analysis data obtained from 36 randomized controlled studies, no significant difference was found between the efficacy and reliability of different sedation methods used in endoscopic procedures (18). In our study, it was observed that the combination of propofol + midazolam + meperidine was the most preferred anesthetic combination, and the second most preferred combination was midazolam + meperidine. We think that anesthesia method is chosen according to the procedure performed, the patient's age, additional diseases and sedation needs.

Different complication rates have been reported in NORA applications, with a rate of 6.2% in a study conducted with 3,583 patients, and 2.8% in another study with 1,622 patients (19,20). There are also studies reporting complications with a rate of 0.17% (21). In our study, the complication rate was found to be 3.95% and minor complications were found to be the majority. It is noteworthy that our number of cases is quite high compared to other studies. We think that these differences in rates are due to differences in the number of patients, patient diversity and the procedures performed.

Despite all preparations, complications may occur in NORA applications. These complications are aspiration, hypothermia, hypoxia, hypovolemia, hypotension, cardiac complications, anaphylaxis, nausea-vomiting, and procedure-related complications (22,23). Metzner et al. (24) emphasized that the rate of death and aspiration pneumonia is more common in NORA applications than in the operating room. In our study, it was found that there were no complications related to death or aspiration in a one-year period. In the same study, it was stated that respiratory complications were more common in NORA applications (44%) than in the operating room (24). In our study, 33 patients (0.18%) had respiratory depression and 559 patients (3.05%) had desaturation. In addition, pneumothorax developed in one patient due to the surgical procedure performed in our study and was treated with underwater chest tube drainage.

Complications of severe hypotension, arrhythmia, and myocardial ischemia can be seen in sedation of elderly ASA III and IV patients with severe comorbidities (25). In our study, bradycardia developed in 47 patients (0.25%) and it was observed that they were treated with atropine. Other cardiac complications were not observed. We think that this result is due to the low rate of ASA III and IV patients in our study and the anesthetic management.

Many centers do not yet have recovery units for NORA applications. This situation causes the patients to be discharged without being recovered sufficiently and the number of cases to be taken during the day to be decreased (26,27). Preventable respiratory complications mostly occur during recovery, so patients should be observed well until a complete recovery (28). There is a recovery room in the endoscopy unit of our hospital and patients with an Aldrete score of 9 or above are sent home. In our study, delay in recovery was observed in 84 patients in endoscopic procedures performed with sedo-analgesia. We think that it causes a delay in recovery after the procedure, depending on the comorbidities of the patients and the drugs and doses used.

Since our study was retrospective, randomization of the cases could not be achieved. For this reason, the number of patients between the groups is not equally distributed. The ages and ASA scores of the patients who underwent interventional procedures in our endoscopy unit differed according to the groups, and no comparison could be made between the anesthetic agent used and the rate of complications. There is a need for prospective, randomized studies with no difference in age groups regarding the NORA applications.

## Conclusion

Anesthesia is required for different interventional procedures, especially gastroscopy, in endoscopy units outside the operating room. Sedation given to patients in these units facilitates the procedure, increases

patient safety and satisfaction as well as physician comfort. NORA applications are similar to the applications in the operating room due to the risks they carry, but in these places more attention should be paid because the patient circulation is very fast. Under suitable conditions, an experienced anesthesiologist with adequate equipment will be able to safely perform NORA procedures. Today, the number of NORA applications has increased. Anesthesiologists should make a sufficient preoperative evaluation of these patients and try to provide appropriate physical conditions in these departments.

### Ethics

**Ethics Committee Approval:** Ethics Committee approval was obtained from University of Health Science Turkey, İstanbul Training and Research Hospital for the study (approval no: 1796, date: 12.04.2019).

**Informed Consent:** Patient information was scanned retrospectively from the anesthesia files; therefore, written consent could not be obtained from the patients for our study.

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

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

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## References


1. Türk Anesteziyoloji ve Reanimasyon Derneği (TARD). Anestezi Uygulama Klavuzları. Ameliyathane Dışı Anestezi Uygulamaları. 2015; Aralık.
2. Thompson AM, Wright DJ, Murray W, Ritchie GL, Burton HD, Stonebridge PA. Analysis of 153 deaths after upper gastrointestinal endoscopy: room for improvement? Surg Endosc 2004; 18: 22-5.
3. Vargo JJ, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, et al. American Association for Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Association Institute. Multisociety sedation curriculum for gastrointestinal endoscopy. Gastrointest Endosc 2012; 76: e1-e25.
4. Karamnov S, Sarkisian N, Grammer R, Gross WL, Urman RD. Analysis of adverse events associated with adult moderate procedural sedation outside the operating room. J Patient Saf 2017; 13: 111-21.
5. Cima RR, Brown MJ, Hebl JR, Moore R, Rogers JC, Kollengode A, et al. Use of lean and six sigma methodology to improve operating room efficiency in a high-volume tertiary-care academic medical center. J Am Coll Surg 2011; 213: 83-92.
6. Harnett MJ, Correll DJ, Hurwitz S, Bader AM, Hepner DL. Improving efficiency and patient satisfaction in a tertiary teaching hospital preoperative clinic. Anesthesiology 2010; 112: 66-72.
7. Bonnet F, Marret E. Anaesthesia outside the operating room: conflicting strategies? Curr Opin Anaesthesiol 2008; 21: 478-9.
8. Ameliyathane Dışında Anestezi. Tüzüner F, editor. Anestezi Yoğun Bakım Ağrı 1st ed. Ankara: MN Medikal ve Nobel Tıp Kitap Sarayı; 2010.p.1127-36.
9. Kayhan Z. Anestezi ve ameliyat öncesi değerlendirme ve hazırlık. Klinik Anestezi. 3rd ed. İstanbul: Logos Yayıncılık; 2007.p.16-36.
10. Korkmaz T, Ateş Y. Ameliyathane dışı anestezi uygulamaları. Editörler: Özatamer O, Alkış N, Batıislam Y, Küçük. Anestezide Güncel Konular. Ankara: Nobel Tıp Kitapevleri; 2002;371-91.
11. Paspatis GA, Manolaraki MM, Vardas E, Theodoropoulou A, Chlouverakis G. Deep sedation for endoscopic retrograde cholangiopancreatography: intravenous propofol alone versus intravenous propofol with oral midazolam premedication. Endoscopy 2008; 40: 308-13.
12. Ghisi D, Fanelli A, Tosi M, Nuzzi M, Fanelli G. Monitored anesthesia care. Minerva Anestesiol 2005; 71: 533-8.
13. Khutia SK, Mandal MC, Das S, Basu SR. Intravenous infusion of ketamine-propofol can be an alternative to intravenous infusion of fentanyl-propofol for deep sedation and analgesia in paediatric patients undergoing emergency short surgical procedures. Indian J Anaesth 2012; 56: 145-50.
14. Roseveare C, Seavell C, Patel P, Criswell J, Shepherd H. Patient-controlled sedation with propofol and alfentanil during colonoscopy: a pilot study. Endoscopy 1998; 30: 482-3.
15. Külling D, Fantin AC, Biro P, Bauerfeind P, Fried M. Safer colonoscopy with patient-controlled analgesia and sedation with propofol and alfentanil. Gastrointest Endosc 2001; 54: 1-7.
16. Poulos JE, Kalogerinis PT, Caudle JN. Propofol compared with combination propofol or midazolam/fentanyl for endoscopy in a community setting. AANA J 2013; 81: 31-6.
17. Horiuchi A, Nakayama Y, Kajiyama M, Kato N, Kamijima T, Ichise Y, et al. Safety and effectiveness of propofol sedation during and after outpatient colonoscopy. World J Gastroenterol 2012; 18: 3420-5.
18. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc 2008; 67: 910-23.
19. Türk HŞ, Aybey F, Ünsal O, Açık ME, Ediz N, Oba S. Ameliyathane dışı anestezi deneyimlerimiz. Şişli Etfal Hastanesi Tıp Bülteni, 2013; 47: 5-10.
20. İyilikci L, Çakmak S, Ögdül E. Ameliyathane dışı anestezi uygulamalarında deneyimlerimiz. Türk Anest Rean Der Dergisi 2006; 34: 169-76.
21. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: A population-based analysis. JAMA Intern Med 2013; 173: 551-6.
22. Melloni C. Morbidity and mortality related to anesthesia outside the operating room. Minerva Anestesiol 2005; 71: 325-34.
23. Missant C, Van de Velde M. Morbidity and mortality related to anaesthesia outside the operating room. Curr Opin Anaesthesiol 2004; 17: 323-7.
24. Metzner J, Posner KL, Domino KB. The risk and safety of anesthesia at remote locations: the US closed claims analysis. Curr Opin Anesthesiol 2009; 22: 502-8.
25. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. World J Gastrointest Endosc 2013; 5: 527-33.
26. Metzner J, Domino KB. Risks of anesthesia or sedation outside the operating room: the role of the anesthesia care provider. Curr Opin Anaesthesiol 2010; 23: 523-31.
27. Pino RM. The nature of anesthesia and procedural sedation outside of the operating room. Curr Opin Anaesthesiol 2007; 20: 293-394.
28. Amornyotin S. Sedation-related complications in gastrointestinal endoscopy. World J Gastrointest Endosc 2013; 5: 527-33.

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# Pseudoexfoliation Syndrome Prevalence in Somali Patients with Senile Cataract

## Senil Kataraktı Olan Somalili Hastalarda Psödoeksfoliasyon Sendromu Prevalansı

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## ABSTRACT

**Introduction:** To evaluate the prevalence and demographic data of Pseudoexfoliation syndrome (PEX) in Somali patients with age-related cataract surgery.

**Methods:** The study included 110 eyes of 110 patients planned for undergoing cataract surgery. Slit lamp biomicroscopy was used for classifying the cataract as nuclear, cortical, mature or hypermature. Goldmann applanation tonometer was used to measure the intraocular pressure. The inclusion criteria were: age >50 years, surgical indication because of age-related cataract (severity of lens opacification ≥2 in Lens Opacity Classification System III) and visual acuity <3/10. Pseudoexfoliation was defined as the presence of a different-looking fibrillar white substance that formed an almost complete ring on the lens surface or on the pupillary edge.

**Results:** The prevalence of PEX was 40.9% (45/110). It was bilateral in 71.1% (32/45) of the cases. The mean age of the sample was 67.4±8.9; however, that of patients with PEX (71.3±7.2 years) was significantly higher than in patients without it (64.7±9 years) ($p<0.05$). The prevalence of PEX was higher in patients with mature cataract ($p<0.05$) and older age ($p=0.01$). Mean intraocular pressure was higher in eyes with pseudoexfoliation syndrome (23.3±3.5 mmHg) than in those without it (14.3±4.2 mmHg); and this finding was statistically significant ($p<0.05$).

**Conclusion:** PEX is a common condition in the Somali population. It is associated with ageing, mature and hypermature type of cataracts, glaucoma and increased intraocular pressure.

**Keywords:** Cataract, PEX, pseudoexfoliation, somalia, sub-saharan africa

## ÖZ

**Amaç:** Yaşa bağlı katarakt cerrahisi planlanan Somalili hastaları da psödoeksfolyasyon sendromu (PEX) prevalansını ve demografik verilerini değerlendirmekti.

**Yöntemler:** Çalışmaya katarakt operasyonu için hazırlanan 110 hastanın 110 gözü dahil edildi. Katarakt tipi, yarık lamba biyomikroskopisi ile nükleer, kortikal, matur veya hipermatur olarak sınıflandırıldı. Hastaların göz içi basıncı, Goldmann aplanasyon tonometresi ile ölçüldü. Çalışmaya dahil edilme kriterleri 50 yaşın üzerinde olma, yaşa bağlı katarakt tanısı nedeni ile cerrahi endikasyonu olma (Lens Opasite Sınıflandırma Sistemi III'de şiddetinin ≥2 olması) ve görme keskinliğinin 3/10'un altında olmasıydı. Psödoeksfoliasyon, lens yüzeyinde veya pupiller kenarda neredeyse tam bir halka oluşturan farklı görünümlü fibriller beyaz bir maddenin varlığı olarak tanımlandı.

**Bulgular:** PEX prevalansı %40,9 idi (45/110). Olguların %71,1'inde (32/45) PEX bilateral idi. Yüz on olgunun ortalama yaşı 67,4±8,9 idi. PEX'li hastaların yaş ortalaması (71,3±7,2 yıl), olmayan hastaların yaş ortalamasından yüksekti (64,7±9 yıl) ve istatistiksel olarak anlamlıydı ($p<0,05$). Matur kataraktlı hastalarda daha fazla PEX mevcuttu ($p<0,05$). Ortalama göz içi basıncı, PEX'li gözlerde (23,3±3,5 mmHg), PEX olmayan gözlere (14,3±4,2 mmHg) göre daha yüksekti ve bu istatistiksel olarak anlamlıydı ($p<0,05$).

**Sonuç:** Somali popülasyonunda PEX sık görülen bir durumdur. PEX yaşlanma, matur ve hipermatur tipte katarakt, glokom ve artmış göz içi basıncı ile ilişkilidir.

**Anahtar Kelimeler:** Katarakt, PEX, psödoeksfoliasyon, somali, sahra altı afrika

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## Introduction

Pseudoexfoliation is a condition characterized by accumulation of extracellular fibrillar material in systemic tissues and eyes.It is present in the eye, on the lens surface, lens zonules, iris surface, corneal endothelium, trabecular meshwork, pupil edge and anterior hyaloid surface (1). Aging is an important risk factor in the development of Pseudoexfoliation syndrome (PEX) and cataracts. The incidence of PEX is positively correlated with age. Increased lens opacity has also been associated with PEX (2).

The presence of PEX is etiologically associated with cataract, lens subluxation, retinal vein occlusion, open-angle glaucoma, and closed-angle glaucoma (3). In addition, it is known that the frequency of complications of zonular detachment, posterior capsule rupture and vitreous loss during cataract extraction in PEX eyes increases compared to normal eyes (4).

Pseudoexfoliation glaucoma is more severe than primary open-angle glaucoma in terms of clinical course and prognosis (5). Pseudoexfoliation glaucoma has much worse visual field and higher optic nerve damage during diagnosis than primary open-angle glaucoma. This may be due to higher and greater fluctuations in pseudoexfoliation glaucoma.

Epidemiological data on the prevalence of PEX is best obtained from population-based research, but useful information on the prevalence of PEX can be obtained from different subgroups of a population such as cases of cataracts and glaucoma (6).

Our clinical observation led us to believe that the prevalence of PEX among Somali people is relatively high. As a result of this situation, we aimed to investigate the prevalence of PEX in a prospective study in Somali patients who were scheduled to undergo cataract surgery.

## Methods

This hospital-based prospective study was conducted according to the principles of the Declaration of Helsinki and received the approval of the Ethics Committee of the Recep Tayyip Erdoğan Training and Research Hospital of Somalia Mogadishu Turkey (decision no: 172, date: 25.11.2019). Written informed consent was obtained from the patients and their families before any examination or treatment was performed.

Our hospital, which is located in Mogadishu, the capital of Somalia and is the only tertiary health center in the country, is a reference hospital where patients are transferred from all over the country and was opened with the help of the Republic of Turkey to serve the entire Somali population. At the same time, the appointment of specialist doctors for the training of Somali assistant doctors is done by the Ministry of health of the Republic of Turkey temporarily and periodically (4 months). During November 2019 - February 2020, 110 eyes of 110 patients admitted to the eye outpatient clinic of Mogadishu Turkey Training and Research Hospital in Somalia with low vision, diagnosed with cataracts and prepared for the operation were included in this study. The age and gender of the patients were recorded. Cataract type of all patients were classified as nuclear, cortical, matur and hypermature by slit lamp biomicroscopy. Intraocular pressure (IOP) was measured with Goldmann aplanation tonometer.

The criteria to be included in the study were; being over 50 years of age, being a surgical indication for age-related cataract diagnosis (intensity ≥2 in Lens Opacite Classification System III) and visual acuity below 3/10. Patients suspected of glaucoma (optic nerve head abnormalities, history of glaucoma and IOP>21 mmHg) were screened for this disease according to the criteria of the International geographical and epidemiological Society of Ophthalmology (7). Patients with a history of eye trauma and/or surgery, congenital cataracts, drug-related cataracts, and uveitis-related cataracts were excluded from the study.

Pseudoexfoliation was described as the presence of a distinctive-looking fibrillar white substance that forms an almost complete ring on the lens surface or pupillary edge (8). All cases were examined by fundus with detailed optic nerve examination. Fully invisible nerves were evaluated using B-mode ultrasonography.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS version 23.0 (SPSS v.23.0, Illinois, USA). Comparisons between the two groups were calculated using the Pearson chi-square test. The frequency analysis was done by chi-square testing. $P<0.05$ was considered statistically significant.

## Results

The prevalence of PEX was 40.9% (45 out of 110 eyes). In 71.1% (32/45) of cases, PEX was bilateral. The mean age of 110 patients was 67.4±8.9 years (51-88 years) (Table 1). The mean age of PEX patients (71.3±7.2 years) was significantly higher than the average age of non-PEX patients

**Table 1. Prevalence of pseudoexfoliation syndrome by gender and age**

| | PEX | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Yes** | **%** | **No** | **%** | **Total** | **%** | **p** |
| 51-60 | 4 | (12.9) | 27 | (87.1) | 31 | (28.2) | <0.05 |
| 61-70 | 13 | (41.9) | 18 | (58.1) | 31 | (28.2) | |
| 71-80 | 25 | (59.5) | 17 | (40.5) | 42 | (38.2) | |
| >80 | 3 | (50) | 3 | (50) | 6 | (5.5) | |
| Mean age | 71.3±7.2 | - | 64.7±9 | - | 67.4±8.9 | - | <0.05 |
| Female | 18 | (36.7) | 31 | (63.3) | 49 | (44.5) | 0.425 |
| Male | 27 | (44.3) | 34 | (55.7) | 61 | (55.5) | |

PEX: Pseudoexfoliation syndrome

(64.7±9 years) ($p<0.05$). PEX prevalence was positively correlated with age increase and this finding was statistically significant ($p=0.01$). PEX was significantly higher in patients with matured cataracts ($p<0.05$). The mean IOP was significantly higher in eyes with PEX (23.3±3.5 mmHg) than eyes without PEX (14.3±4.2 mmHg) ($p<0.05$). Patients with IOP >21 mmHg and glaucoma were higher in the PEX group and statistically significant ($p<0.05$) (Table 2).

## Discussion

Our study is the first study on PEX in Somalia. In this study, the frequency of PEX was 40.9% in patients preparing for cataract surgery. This finding was higher compared to other studies conducted in different populations. The prevalence of PEX was 10.7% (7) in Iceland, 16.4% (9) in Turkey, 22.1% (10) in India, 25.2% (11) in Finland, 27.9% (12) in Greece and 39.3% (6) in Ethiopia. To date, many researchers have reported significant differences in the prevalence of PEX in the same country or close geographic area (13,14). The reason for the large change in PEX prevalence in near and far populations is unclear. There have been studies (15) showing that exposure to ultraviolet radiation increases prevalence, but the high prevalence among Icelanders living near the North Pole does not support this hypothesis (16).

There was no significant difference in the gender distribution of PEX syndrome in our study, and this finding was similar to other studies in Japan (17), Australia (18) and Saudi Arabia (1). However, some research has indicated that it is more common in men and has linked this condition to men working more outdoors and being more exposed to ultraviolet radiation (19,20).

Our study included patients over the age of 50 with PEX findings. In a hospital-based study that investigated the frequency of PEX in patients preparing for cataract surgery, it was reported that PEX was not seen under the age of 50 (21). In addition, hard cataracts are more common over the age of 50 (21). In our study, PEX frequency was 12.9% in the 51-60 age group, 41.9% in the 61-70 age group, 59.5% in the 71-80 age group and 50% in the over 80 age group. The increase in PEX frequency relative to age was statistically significant ($p<0.05$).

PEX patients in our study were significantly older than non-PEX patients. This finding was similar to the results of earlier research (13,22). Compared to study results from other regions, PEX appears to occur at a relatively younger age in Africans (4). However, the average age of the patients with PEX was similar to the European average (23). One of the reasons that the age of the patients in our study was higher than in other studies in Africa is that Somali patients were often admitted to hospital for cataract surgery when their vision level was too low to do daily work. The most common type of cataract in our PEX patients was hypermature cataract (55.5%), while in non-PEX patients (41.5%), cortical cataract was the most common type. The proportion of mature and hypermature cataracts (49.1%) was high due to late application. The increase in PEX rate was statistically significant as cataract stiffness increased ($p<0.05$).

Although the relationship between PEX and cataract is not fully explained, some theories have been presented. The most widely accepted theory is that hypoxia, oxidative stress, ocular ischemia developing as a result of increased growth factor levels in aqueous fluid due to deterioration of the blood-aqueous fluid barrier and that this condition contributes simultaneously to the development of PEX and cataract (24).

Today, the relationship between PEX and glaucoma is well known. The prevalence of glaucoma in PEX patients was 13.3% (6) in Ethiopia, 19% (25) in South Africa, 28.8% (26) in Greece, 32.1% (9) in Turkey and 71% in our study. The most important reason for this high rate in our study is that our institution is the only tertiary Hospital in the country and that patients with complicated cataracts that cannot be done in other centers are referred to our hospital.

Additionally, the average IOP was higher in PEX patients than in the non-PEX group, which was consistent with previous studies (2,13,26) and statistically significant ($p<0.05$). Based on these findings, the presence of PEX can be considered one of the main risk factors in the development of glaucoma.

The limitation of our study was that it was a hospital-based study and that the prevalence of PEX was assessed only in the population with cataracts. Therefore, the results of the study may not reflect the actual distribution of PEX in the Somali general population. Prospective community-based studies are needed to determine the optimal frequency of PEX in this area.

## Conclusion

Our study confirms that PEX is a common condition in the Somali public. In our study, PEX was associated with aging, matured and hypermature type cataracts, glaucoma and increased IOP.

**Table 2. Characteristics of Pseudoexfoliation syndrome and non-Pseudoexfoliation syndrome eyes (number of patients =110)**

| | PEX | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Yes** | **%** | **No** | **%** | **Total** | **%** | **p** |
| Cortical cataract | 3 | (10) | 27 | (90) | 30 | (27.3) | <0.05 |
| Nuclear cataract | 4 | (84.6) | 22 | (15.4) | 26 | (23.6) | |
| Mature cataract | 13 | (56.5) | 10 | (43.5) | 23 | (20.9) | |
| Hypermature cataract | 25 | (80.6) | 6 | (19.4) | 31 | (28.2) | |
| IOP (mmHg) | 23.3±3.5 | - | 14.3±4.2 | - | 18±5.9 | - | <0.05 |
| Glaucoma (+) | 32 | (71.1) | 7 | (89.2) | 39 | (35.5) | <0.05 |
| Glaucoma (-) | 13 | (28.9) | 58 | (10.8) | 71 | (64.5) | |

PEX: Pseudoexfoliation syndrome, IOP: intraocular pressure

### Ethics

**Ethics Committee Approval:** This hospital-based prospective study was conducted according to the principles of the Declaration of Helsinki and received the approval of the Ethics Committee of the Recep Tayyip Erdoğan Training and Research Hospital of Somalia Mogadishu Turkey (decision no: 172, date: 25.11.2019).

**Informed Consent:** Written informed consent was obtained from the patients and their families before any examination or treatment was performed.

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

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## References

1. Al-Saleh S, Al-Dabbagh N, Al-Shamrani S, Khan N, Arfin M, Tariq M, et al. Prevalence of ocular pseudoexfoliation syndrome and associated complications in Riyadh, Saudi Arabia. Saudi Med J 2015; 36: 108-12.
2. Kaljurand K, Puska P. Exfoliation syndrome in Estonian patients scheduled for cataract surgery. Acta Ophthalmol Scand 2004; 82: 259-63.
3. Ritch R, Schlötzer-Schrehardt U. Exfoliation Syndrome. Surv Ophthalmol 2001; 45: 265-315.
4. Olawoye OO, Pasquale LR, Ritch R. Exfoliation syndrome in sub-Saharan Africa. Int Ophthalmol [Internet] 2014; 34: 1165-73.
5. Futa R, Shimizu T, Furuyoshi N, Nishiyama M, Hagihara O. Clinical features of capsular glaucoma in comparison with primary open-angle glaucoma in Japan. Acta Ophthalmol (Copenh) 2009; 70: 214-9.
6. Teshome T, Regassa K. Prevalence of pseudoexfoliation syndrome in Ethiopian patients scheduled for cataract surgery. Acta Ophthalmol Scand 2004; 82: 254-8.
7. Arnarsson A, Damji KF, Sverrisson T, Sasaki H, Jonasson F. Pseudoexfoliation in the Reykjavik Eye Study: prevalence and related ophthalmological variables. Acta Ophthalmol Scand 2007; 85: 822-7.
8. Schlötzer-Schrehardt U, Naumann GOH. Ocular and Systemic Pseudoexfoliation Syndrome. Am J Ophthalmol 2006; 141: 921-37.
9. Sekeroglu MA, Bozkurt B, Irkec M, Ustunel S, Orhan M, Saracbasi O. Systemic Associations and Prevalence of Exfoliation Syndrome in Patients Scheduled for Cataract Surgery. Eur J Ophthalmol 2008; 18: 551-5.
10. Joshi R, Singanwad S. Frequency and surgical difficulties associated with pseudoexfoliation syndrome among Indian rural population scheduled for cataract surgery: Hospital-based data. Indian J Ophthalmol 2019; 67: 221-6.
11. Hietanen J, Kivelä T, Vesti E, Tarkkanen A. Exfoliation syndrome in patients scheduled for cataract surgery. Acta Ophthalmol (Copenh) 2009; 70: 440-6.
12. Andrikopoulos GK, Mela EK, Georgakopoulos CD, Papadopoulos GE, Damelou AN, Alexopoulos DK, et al. Pseudoexfoliation syndrome prevalence in Greek patients with cataract and its association to glaucoma and coronary artery disease. Eye 2009; 23: 442-7.
13. Wålinder P-EK, Olivius EOP, Nordell SI, Thorburn WE. Fibrinoid reaction after extracapsular cataract extraction and relationship to exfoliation syndrome. J Cataract Refract Surg 1989; 15: 526-30.
14. Ritland JS, Egge K, Lydersen S, Juul R, Semb SO. Exfoliative glaucoma and primary open-angle glaucoma: associations with death causes and comorbidity. Acta Ophthalmol Scand 2004; 82: 401-4.
15. Pasquale LR, Jiwani AZ, Zehavi-Dorin T, Majd A, Rhee DJ, Chen T, et al. Solar Exposure and Residential Geographic History in Relation to Exfoliation Syndrome in the United States and Israel. JAMA Ophthalmol 2014; 132: 1439-45.
16. Arnarsson ÃM. Epidemiology of exfoliation syndrome in the Reykjavik Eye Study. Acta Ophthalmol 2009; 87: 1-17.
17. Miyazaki M, Kubota T, Kubo M, Kiyohara Y, Iida M, Nose Y, et al. The Prevalence of Pseudoexfoliation Syndrome in a Japanese Population. J Glaucoma 2005; 14: 482-4.
18. Mccarty CA, Taylor HR. Pseudoexfoliation syndrome in Australian adults. Am J Ophthalmol 2000; 129: 629-33.
19. Al-Shaer M, Bamashmus M, Al-Barrag A. Point prevalence of pseudoexfoliation syndrome in patients scheduled for cataract surgery in eye camps in yemen. Middle East Afr J Ophthalmol 2010; 17: 74-7.
20. Idakwo U, Olawoye O, Ajayi BG, Ritch R. Exfoliation syndrome in Northern Nigeria. Clin Ophthalmol 2018; 12: 271-7.
21. Govetto A, Lorente R, de Parga PV, Rojas L, Moreno C, Lagoa F, et al. Frequency of pseudoexfoliation among patients scheduled for cataract surgery. J Cataract Refract Surg 2015; 41: 1224-31.
22. Konstas AGP, Tsironi S, Ritch R. Current concepts in the pathogenesis and management of exfoliation syndrome and exfoliative glaucoma. Compr Ophthalmol Update 2006; 7: 131-41.
23. Anastasopoulos E, Topouzis F, Wilson MR, Harris A, Pappas T, Yu F, et al. Characteristics of Pseudoexfoliation in the Thessaloniki Eye Study. J Glaucoma 2011; 20: 160-6.
24. Damji KF, Bains HS, Stefansson E, Loftsdottir M, Sverrisson T, Thorgeirsson E, et al. Is pseudoexfoliation syndrome inherited? A review of genetic and nongenetic factors and a new observation. Ophthalmic Genet 1998; 19: 175-85.
25. Bartholomew RS. Pseudocapsular exfoliation in the Bantu of South Africa. II. Occurrence and prevalence. Br J Ophthalmol 1973; 57: 41-5.
26. Kozobolis VP, Papatzanaki M, Vlachonikolis IG, Pallikaris IG, Tsambarlakis IG. Epidemiology of pseudoexfoliation in the island of Crete (Greece). Acta Ophthalmol Scand 2009; 75: 726-9.

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# Prognostic Value of Preoperative Neutrophil-lymphocyte/Platelet-lymphocyte Ratio in Patients with Stage II-III Rectal Cancer Who Underwent Curative Resection

## Küratif Rezeksiyon Uygulanan Evre II-III Rektum Kanserli Hastalarda Preoperatif Nötrofil-lenfosit/Trombosit-lenfosit Oranının Prognostik Değeri

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## ABSTRACT

**Introduction:** This study aimed to evaluate the prognostic value and survival effects of the neutrophil-lymphocyte/platelet-lymphocyte ratio (NLR/PLR) in the preoperative peripheral blood count of patients who underwent curative resection due to stage II-III rectal cancer.

**Methods:** Between 2011 and 2017, a total of 156 patients with stage II-III rectal cancer who underwent curative resection were evaluated. Before the curative resection, complete blood counts were obtained within 3 days. The last follow-up was in December 2018. NLR and PLR were calculated by dividing the absolute neutrophil or platelet count by the absolute lymphocyte count, respectively.

**Results:** Postoperatively, adenocarcinoma histology (p=0.025), R1 resection (p<0.001), T4 stage (p=0.001), N stage positivity (p=0.003), tumor-node-metastasis (TNM) stage III disease (p=0.002), presence of lenfovascular invasion (p<0.001), presence of perineural invasion (p<0.001), preoperative NLR ≥3.6 (p<0.001) and PLR ≥192 (p<0.001) were identified in the rectal cancer patients as factors that influence survival in univariate analysis. In our study, R1 resection [hazard ratio (HR): 0.341; 95% confidence interval (CI): 0.157-0.740; p=0.007]; T4 stage (HR: 0.261; 95% CI: 0.129-0.527; p<0.001), N0 stage vs N1 positivity (HR: 0.071; 95% CI: 0.010-0.525; p=0.010), N0 stage vs N2 positivity (HR: 0.068; 95% CI: 0.008-0.565; p=0.013), presence of metastases (HR: 0.130; 95% CI: 0.054-0.309, p<0.001), TNM stage III (HR: 0.261; 95% CI: 0.129-0.527, p<0.001) and preoperative NLR ≥3.6 (HR: 0.378; 95% CI: 0.154-0.930, p=0.034) were identified as independent factors affecting survival in multivariate analysis.

## ÖZ

**Amaç:** Bu çalışmada evre II-III rektum kanseri ile küratif rezeksiyon uygulanan hastalarda preoperatif periferik kan sayımlarında nötrofil-lenfosit/trombosit-lenfosit oranının (NLO/PLO) prognostik değeri ve sağkalım etkilerinin değerlendirilmesi amaçlanmıştır.

**Yöntemler:** 2011-2017 yılları arasında küratif rezeksiyon uygulanan evre II-III rektum kanserli 156 hasta değerlendirildi. Küratif rezeksiyondan önce, tam kan sayımı 3 gün içinde elde edildi. Son takip Aralık 2018 oldu. NLO ve PLO, mutlak nötrofil veya trombosit sayısının mutlak lenfosit sayısına bölünmesiyle hesaplandı.

**Bulgular:** Postoperatif olarak, rektum kanseri hastalarında adenokarsinom histolojisi (p=0,025), R1 rezeksiyonu (p<0,001), T4 evre (p=0,001), N evre pozitifliği (p=0,003), tümör-nod-metastaz (TNM) evre 3 hastalığı (p=0,002), lenfovasküler istila varlığı (p<0,001), perinöral invazyon varlığı (p<0,001), preoperatif NLO ≥3,6 (p<0,001) ve PLO ≥192 (p<0,001) univariate analizde sağkalımı etkileyen faktörler olarak tanımlanmıştır. Çalışmamızda R1 rezeksiyonu [tehlike oranı (HR): 0,341; %95 güven aralığı (GA): 0,157-0,740; p=0,007]; T4 evresi (HR: 0,261; %95 GA: 0,129-0,527; p<0,001), N0'a karşı N1 pozitifliği (HR: 0,071; %95 GA: 0,010-0,525; p=0,010), N0'a karşı N2 pozitifliği (HR: 0,068; %95 CI: 0,008-0,565; p=0,013), metastaz varlığı (HR: 0,130; %95 GA: 0,054-0,309, p<0,001), TNM evre III (HR: 0,261; %95 GA: 0,129-0,527, p<0,001) ve preoperatif NLR ≥3,6 (HR: 0,378; %95 GA: 0,154-0,930, p=0,034) multivariate analizde sağkalımı etkileyen bağımsız faktörler olarak tanımlandı.

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**Conclusion:** In our study, due to the low cost, it extensive use, and association with overall survival, NLR was found to be a better prognostic marker. Besides, R1 resection, T4 stage, lymph node positivity, presence of metastases, TNM stage III were found to be prognostic factors that negatively affect overall survival. NLR is a biomarker that is thought to be an indicator of the systemic inflammatory response and can be easily obtained as a prognostic biomarker candidate.

**Keywords:** Stage II, III rectum cancer, neutrophil-lymphocyte, platelet-lymphocyte ratio, prognosis

**Sonuç:** Çalışmamızda, düşük maliyetli, yaygın olarak kullanılan, genel sağkalım ile ilişkili, NLO'nun daha iyi bir prognostik belirteç olduğu bulunmuştur. Ayrıca R1 rezeksiyon, T4 evresi, lenf nodu pozitifliği, metastaz varlığı, TNM evre III genel sağkalımı olumsuz etkileyen prognostik faktörler olarak bulundu. NLO sistemik enflamatuvar yanıtın bir göstergesi olduğu düşünülen ve prognostik biyobelirteç adayı olarak kolayca elde edilebilen bir biyobelirteçtir.

**Anahtar Kelimeler:** Evre II, III rektum kanseri, nötrofil-lenfosit, trombosit-lenfosit oranı, prognoz

## Introduction

Colorectal cancers is the third most common cancer in the world. Surgery is chosen for the treatment of non-metastatic diseases and postoperative treatment is usually managed according to the tumor-node-metastasis (TNM) staging system (1). Cancer-related inflammation, tumour and host- derived cytokines, immune cells and small inflammatory protein agents cover leukocytes, neutrophils, lymphocytes and platelets and is determined by the levels of acute-phase proteins (2,3). Lymphocytes play a crucial role in cytotoxic cell death and cytokine production, which prevents proliferation and metastasis of malignant cells (4). Elevated neutrophil count increases tumour growth and metastasis by remodelling the extracellular matrix, thereby releasing reactive oxygen species and suppressing lymphocyte activity (5). Also, the presence of tumour cells affects platelets and causes cancer-related thrombosis (6). Platelets excrete growth factors that support tumour growth, angiogenesis and metastasis (7). Increased NLR seems to be related with a poor prognosis in different cancers (8-11). We know that patients at an equal stage can have separate clinical features and outcomes. In clinical practice, simple methods such as NLR added to TNM staging can help with this situation to create an individualised treatment strategy.

We aimed to evaluate the prognostic value and survival effects of the neutrophil-lymphocyte ratio (NLR)/platelet-lymphocyte ratio (PLR) in the preoperative peripheral blood counts of patients who underwent curative resection with stage II-III rectal cancer.

## Methods

A total of 156 patients with stage II-III rectal cancer who underwent curative resection between 2011 and 2017 were evaluated. The last follow-up was in December 2018. Before the curative resection, complete blood count were obtained within 3 days. Complete blood count was performed with XN-900 Haematology analyser (Symex, Japan). The normal reference range for lymphocytes was $1.18\text{-}3.57\times10^9$/L, for neutrophils $1.56\text{-}6.13\times10^9$/L and platelets for $142\text{-}424\times10^9$/L. We determined the cut-off with the receiver operating characteristic curve for NLR 3.6 [area under the curve (AUC): 0.791; 95% confidence interval (CI): 0.711-0.872; $p<0.001$] and PLR 192 (AUC: 0.784; 95% CI: 0.704-0.864; $p<0.001$). Colonoscopy and biopsy were performed to diagnose all the patients preoperatively. For staging, a computed tomography (CT) scan of the thorax and abdomen or an 18-florodeoksiglukoz positron emission tomography CT was performed. Pelvic magnetic resonance imaging for local disease staging was performed. R0 resection has no postoperative residual tumour and R1 resection has been accepted as the presence of the microscopic residual tumour. In 25-28 fraction, daily dose of 180-200 cGy, 5,000-5,040 cGy, 5-6 weeks, radiotherapy (RT) was applied. From the first day of RT, continuous bolus infusion 5-FU (225 mg/m$^2$) or 5-FU (425 mg/m$^2$) + calcium leucovorin (20 mg/m$^2$) was given throughout RT. T-test or Mann-Whitney U test were used for non-categorical variables; chi-square and Fisher's exact tests were used for categorical variables. Categorical variables were presented as absolute numbers and percentage values for the NLR and PLR. Prognostic values of each variable were evaluated with univariate and multivariate Cox proportional regression analyses. Overall survival (OS) was calculated and compared using the Kaplan-Meier method and Log-rank test. Inclusion criteria of patients: (1) primary rectal cancer diagnosed in the postoperative stage II,III; (2) patients undergoing radical surgery without neoadjuvant therapy; (3) those with complete blood count and follow-up data. Exclusion criteria were as follows: (1) the presence of infection or haematological disease; (2) to apply neoadjuvant radiochemotherapy first; (3) to have emergency surgery due to bowel obstruction; (4) synchronous/metacron other than cancers; (5) use of anti-inflammatory or immunosuppressive drugs; (6) except neuroendocrine tumours.

### Statistical Analysis

Statistical analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL, USA). A p-value of less than 0.05 from a two-tailed test was considered statistically significant. This study was approved by University Health Sciences Turkey, İstanbul Training and Research Hospital's Ethics Committee (decision no: 2244/ date: 27.04.2020). Due to the retrospective design of the study, informed consent was not obtained from the patients.

## Results

The median age was 61 (range: 22-83). The median tumour diameter was 5.06±1.85 cm (range: 2-12.5). Of our patients, 71 (46%) were females and 85 (54%) were males. Male/female ratio was 1.1/.ost of our patients were located in the upper rectum (n 95; 61%). Thirty-one (20% in the middle rectum and 30 (19%) in the lower rectum. One hundred and twenty-six (81%) patients were operated by low anterior resection and 30 (19%) by abdominoperineal resection. One hundred and nineteen (76%) patients were adenocancers, 20 (13%) patients were mucinous cancers, 16 (11%) patients were in mixed type (adenocancer + mucinous) histology. There were 7 (5%) patients who did not apply RT and 4 (3%) patients who did not use chemotherapy. Liver metastasis was detected in 17 (11%)

patients, lung metastasis in 17 (11%) patients, local recurrence in 14 (9%) patients and peritoneal metastasis in 14 (9%) patients. The number of patients with fewer than 12 lymph nodes removed during surgery was 28 (18%). Since carcinoembryonic antigen was not assessed in all the patients (only 94 patients were evaluated), we did not evaluate the survival with tumour markers in our study. The general characteristics of the patients are shown in Table 1.

NLR ≥3.6 values were in present 68 (44%) patients and PLR ≥192 values in 72 (46%) patients. According to NLR <3.6 vs NLR ≥3.6 and PLR <192 vs PLR ≥192, lymph node involvement, TNM stage III, lenfovascular invasion (LVI) and perineural invasion (PNI) were statistically significant. The demographic comparisons of the patients according to NLR and PLR values are shown in Table 2.

**Table 1. General demographics of patients (lenfovascular invasion, perineural invasion, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio)**

| | Number of patients | % |
|---|---|---|
| **Age (median ± SD)** | 61±12.29 | - |
| **Gender** | | |
| Female | 71 | 45 |
| Male | 85 | 55 |
| **Histology** | | |
| Adenocancer | 119 | 76 |
| Others | 37 | 24 |
| **LVI** | | |
| Absent | 80 | 51 |
| Present | 76 | 49 |
| **PNI** | | |
| Absent | 95 | 61 |
| Present | 61 | 39 |
| **Surgical resection** | | |
| R1 | 23 | 15 |
| R0 | 133 | 85 |
| **T stage** | | |
| 2 | 13 | 8 |
| 3 | 110 | 71 |
| 4 | 33 | 21 |
| **N stage** | | |
| 0 | 66 | 42 |
| 1 | 57 | 37 |
| 2 | 33 | 21 |
| **TNM Stages** | | |
| II | 63 | 40 |
| III | 93 | 60 |
| **Metastases** | | |
| Absent | 94 | 60 |
| Present | 62 | 40 |
| **NLR** | | |
| NLR <3.6 | 88 | 56 |
| NLR ≥3.6 | 68 | 44 |
| **PLR** | | |
| PLR <192 | 84 | 54 |
| PLR ≥192 | 72 | 46 |

NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LVI: lenfovascular invasion, PNI: perineural invasion, SD: standard deviation, TNM: tumor-node-metastasis

Postoperatively, adenocarcinoma histology (p=0.025), R1 resection (p<0.001), T4 stage (p=0.001), N stage positivity (p=0.003), TNM stage III disease (p=0.002), presence of LVI (p<0.001), presence of PNI (p<0.001), preoperative NLR ≥3.6 (p<0.001) and PLR ≥192 (p<0.001) were identified as factors in rectal cancer patients that influence survival in univariate analysis.

In our study, R1 resection [hazard ratio (HR): 0.341; 95% CI: 0.157-0.740; p=0.007)]; T4 stage (HR: 0.261; 95% CI: 0.129-0.527; p<0.001), N0 stage vs N1 positivity (HR: 0.071; 95% CI: 0.010-0.525; p=0.010), N0 stage vs N2 positivity (HR: 0.068; 95% CI: 0.008-0.565; p=0.013), presence of metastases (HR: 0.130; 95% CI: 0.05-0.309, p<0.001), TNM stage III (HR: 0.261; 95% CI: 0.129-0.527, p<0.001) and preoperative NLR ≥3.6 (HR: 0.378; 95% CI: 0.154-0.930, p=0.034) were identified as independent factors affecting survival in multivariate analysis (Table 3).

The 5-year OS was 70 % for stage II and 46% for stage III (Figure 1).

## Discussion

There are many factors that impact the prognosis of colorectal cancer, due to its tumour heterogeneity (12). Colorectal cancer (CRC) risk increases with age (13). In this study, the median age was found as 61 years. Like in our study, the distribution of gender was nearly equal as in other studies. There was a mild male dominance (14,15). Adenocarcinoma is the most familiar histological subtype of CRC, while the mucinous and signet ring cell subtypes are more common in younger patients (16).

In rectal cancer, R1 resection is an independent risk factor that negatively affects the OS. Neoadjuvant RT decreases R1 resection and we have to avoid R1 resection (17,18). We also found that R1 resection was an independent risk factor that shortens the OS.

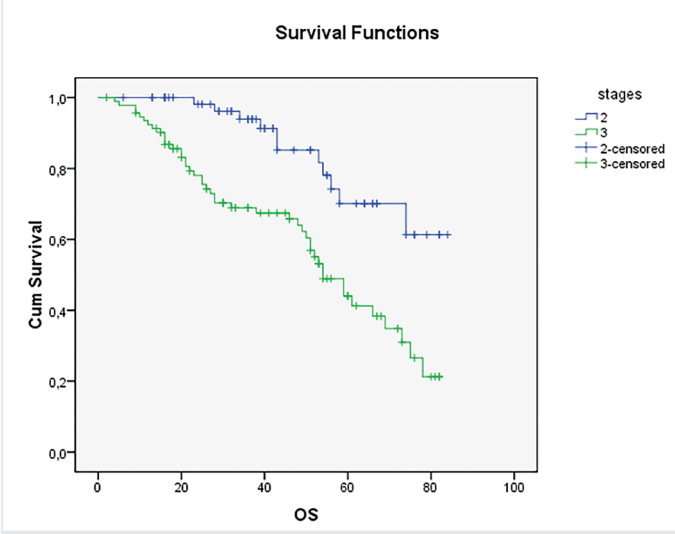


**Figure 1.** OS, according to stage II and stage III (Log-rank p<0.001)

OS: Overall survival

**Table 2. General characteristics of the patients according to neutrophil-lymphocyte ratio and platelet-lymphocyte ratio**

| | NLR <3.6 | NLR ≥3.6 | p | PLR ≥192 | PLR ≥192 | p |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| <65 | 52 | 41 | 0.879 | 47 | 46 | 0.314 |
| ≥65 | 36 | 27 | - | 37 | 26 | - |
| **Gender** | | | | | | |
| Female | 42 | 29 | 0.527 | 37 | 34 | 0.691 |
| Male | 46 | 39 | - | 47 | 38 | |
| **Histology** | | | | | | |
| Adenocancer | 71 | 48 | 0.142 | 68 | 51 | 0.139 |
| Others | 17 | 20 | - | 16 | 21 | |
| **LVI** | | | | | | |
| Absent | 56 | 24 | <0.001 | 53 | 27 | 0.001 |
| Present | 32 | 44 | - | 31 | 45 | - |
| **PNI** | | | | | | |
| Absent | 64 | 31 | 0.001 | 63 | 32 | <0.001 |
| Present | 24 | 37 | - | 21 | 40 | - |
| **Surgical resection** | | | | | | |
| R1 | 7 | 16 | 0.007 | 9 | 14 | 0.125 |
| R0 | 81 | 52 | - | 75 | 58 | - |
| **T stage** | | | | | | |
| 2-3 | 73 | 50 | 0.153 | 70 | 53 | 0.138 |
| 4 | 15 | 18 | - | 14 | 19 | - |
| **N stage** | | | | | | |
| 0 | 47 | 19 | - | 48 | 18 | - |
| 1-2 | 41 | 49 | 0.001 | 36 | 54 | <0.001 |
| **TNM stages** | | | | | | |
| II | 45 | 18 | 0.002 | 46 | 17 | <0.001 |
| III | 43 | 50 | - | 38 | 55 | - |
| **Metastases** | | | | | | |
| Absent | 72 | 22 | <0.001 | 68 | 26 | <0.001 |
| Present | 16 | 46 | - | 16 | 46 | - |

NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LVI: lenfovascular invasion, PNI: perineural invasion, TNM: tumor-node-metastasis

In the analysis of 1,437 patients who underwent curative surgery and were diagnosed with stage II-III colorectal cancer, LVI and PNI were found to be independent prognostic factors affecting OS (19). In a recent study investigating the importance of perineural and lymphovascular invasion in locally advanced rectal cancer, PNI was determined as the independent prognostic factor that presented the OS compared to LVI (20). In the univariate analysis in this study, LVI and PNI were found to be statistically significant, but were not prognostic.

In a study with 508 patients undergoing radical surgery, degree of differentiation, age, T stage, nodal involvement, PNI were identified as independent prognostic factors affecting OS (21). Nodal involvement and advanced T stage were independent prognostic factors negatively affecting the OS, as in our study.

The TNM staging system directs us the clinicians to choose the appropriate treatment for the patient and is standard. According to the American Joint Committee of Cancer-7 rectal cancer staging system, a minimum of 12 lymph nodes are required for the suitable tumour stage and is involved with a good OS in patients treated with surgery (22). In our study, less than 12 lymph nodes were removed in 18% of the patients, which did not affect the OS. In another study, NLR and PLR both demonstrated their potential significance for the TNM stage assessment in CRC patients (23). The increase in NLR was also related to the TNM stages in our study.

A study evaluating 205 surgical CRC patients concluded that preoperative high NLR is an independent prognostic marker for OS and cancer-specific survival (24). In a retrospective evaluation of 300 patients and in another study with 200 patients who underwent curative resection for CRC, NLR and PLR were found as independent prognostic factors that negatively impacted the OS (25,26). In our study, only NLR was an independent prognostic factor.

**Table 3. Univariate and multivariate analysis for overall survival**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | **HR** | **%95 CI** | **p** | **HR** | **%95 CI** | **p** |
| **Age** | | | | | | |
| <65 | - | 1 | - | - | - | - |
| ≥65 | 0.924 | 0.537-1.591 | 0.776 | - | - | NI |
| **Gender** | | | | | | |
| Female | - | 1 | - | - | - | - |
| Male | 0.846 | 0.488–1.468 | 0.533 | - | - | NI |
| **Histology** | | | | | | |
| Adenocancer | - | 1 | - | - | 1 | - |
| Others | 0.514 | 0.288-0.919 | 0.025 | 0.546 | 0.279-1.068 | 0.077 |
| **LVI** | | | | | | |
| Absent | - | 1 | - | - | 1 | - |
| Present | 0.355 | 0.202-0.624 | <0.001 | 0.917 | 0.422-1.991 | 0.826 |
| **PNI** | | | | | | |
| Absent | - | 1 | - | - | 1 | - |
| Present | 0.243 | 0.137-0.430 | <0.001 | 0.721 | 0.356-1.458 | 0.362 |
| **Surgical resection** | | | | | | |
| R0 | - | 1 | - | - | 1 | - |
| R1 | 0.264 | 0.141-0.495 | <0.001 | 0.341 | 0.157-0.740 | 0.007 |
| **T stage** | | | | | | |
| T2-3 | - | 1 | - | - | 1 | - |
| T4 | 0.370 | 0.206-0.663 | 0.001 | 0.261 | 0.129-0.527 | <0.001 |
| **N stage** | | | | | | |
| 0 | - | 1 | - | - | 1 | - |
| 1 | 2.539 | 1.249-5.163 | 0.010 | 0.071 | 0.010-0.525 | 0.010 |
| 2 | 5.496 | 2.625-11.50 | <0.001 | 0.068 | 0.008-0.565 | 0.013 |
| **TNM stages** | | | | | | |
| II | - | 1 | - | - | 1 | - |
| III | 0.367 | 0.193-0.699 | 0.002 | 0.098 | 0.013-0.710 | 0.022 |
| **Metastases** | | | | | | |
| Absent | - | 1 | - | - | 1 | - |
| Present | 0.089 | 0.044-0.183 | <0.001 | 0.130 | 0.054-0.309 | <0.001 |
| **NLR** | | | | | | |
| NLR <3.6 | - | 1 | - | - | 1 | - |
| NLR ≥3.6 | 0.180 | 0.096-0.338 | <0.001 | 0.378 | 0.154-0.930 | 0.034 |
| **PLR** | | | | | | |
| PLR <192 | - | 1 | - | - | 1 | - |
| PLR ≥192 | 0.183 | 0.096-0.349 | <0.001 | 0.509 | 0.218-1.188 | 0.118 |

NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, LVI: lenfovascular invasion, PNI: perineural invasion, CI: confidence interval, TNM: tumor-node-metastasis, NI: not included, HR: hazard ratio

In many studies, inflammatory responses have been evaluated with haematological markers. In colorectal cancer, lymphocytes play a significant role in the immune response. Cellular immunity decreases in the presence of systemic inflammation. This promotes a decrease in CD4 lymphocytes and an increase in CD8 suppressor T lymphocytes. Lymphocytes commonly play a considerable role in the growth and progression of cancer via regulation of cell-mediated immunity. Myeloid growth factors are produced by tumours, which may increase the number of neutrophilic granulocytes at the site of the tumour (26). Platelets are taken into the tumour microenvironment and release platelet-induced growth factor and transformative growth factor to enable tumour growth. It regulates angiogenesis and protects tumour

cells from host immune surveillance and direct cellular contact with natural killer cells by forming a network with fibrin surrounding tumour cells during haematogenous propagation (27). Tumour cells can manipulate platelet activity to optimise tumour growth, proliferation, survival and metastasis.

The retrospective character of our study, the frequent use of neoadjuvant chemo RT in patients with rectal cancer nowadays and the small number of patients constitutes our limitations.

## Conclusion

In our study, due to its low cost, extensive use and association with OS, NLR was found to be a better prognostic marker. Besides, R1 resection, T4 stage, lymph node positivity, presence of metastases, TNM stage III were found to be prognostic factors that negatively affect OS. NLR is a biomarker that is thought to be an indicator of the systemic inflammatory response and can be easily obtained as a prognostic biomarker candidate.

### Ethics

**Ethics Committee Approval:** This study was approved by University Health Sciences Turkey, İstanbul Training and Research Hospital's Ethics Committee (decision no: 2244/ date: 27.04.2020).

**Informed Consent:** Due to the retrospective design of the study, informed consent was not obtained from the patients.

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

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

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## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
2. West NR, McCuaig S, Franchini F, Powrie F. Emerging cytokine networks in colorectal cancer. Nat Rev Immunol 2015; 15: 615-29.
3. Shalapour S, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. J Clin Invest 2015; 125: 3347-55.
4. Mallappa S, Sinha A, Gupta S, Chadwick SJ. Preoperative neutrophil to lymphocyte ratio >5 is a prognostic factor forrecurrent colorectal cancer. Colorectal Dis 2013; 15: 323-8.
5. Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013; 30: 432.
6. Goubran HA, Stakiw J, Radosevic M, Burnouf T. Platelet-cancer interactions. Semin Thromb Hemost 2014; 40: 296-305.
7. Goubran HA, Stakiw J, Radosevic M, Burnouf T. Platelets effects on tumor growth. Semin Oncol 2014; 41: 359-69.
8. Maeda K, Shibutani M, Otani H, Nagahara H, Ikeya T, Iseki Y, et al. Inflammation-based factors and prognosis in patients with colorectal cancer. World J Gastrointest Oncol 2015; 7: 111-7.
9. Graziosi L, Marino E, De Angelis V, Rebonato A, Cavazzoni E, Donini A. Prognostic value of preoperative neutrophils to lymphocytes ratio in patients resected for gastric cancer. Am J Surg 2015; 209: 333-7.
10. Sellers CM, Uhlig J, Ludwig JM, Stein SM, Kim HS. Inflammatory markers in intrahepatic cholangiocarcinoma: Effects of advanced liver disease. Cancer Med 2019 ; 8: 5916-29.
11. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal 2019; 33: e22964.
12. Sagaert X, Vanstapel A, Verbeek S. Tumor heterogeneity in colorectal cancer: what do we know so far? Pathobiology 2018; 85: 72-84.
13. Pinsky PF, Schoen RE. Colorectal cancer incidence by age among patients undergoing surveillance colonoscopy. JAMA Intern Med 2015; 175: 858-60.
14. Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. Int J Cancer 2011; 128: 1668-75.
15. Nakagawa H, Ito H, Hosono S, Oze I, Mikami H, Hattori M, et al. Changes in trends in colorectal cancer incidence rate by anatomic site between 1978 and 2004 in Japan. Eur J Cancer Prev 2017; 26: 269-76.
16. Tan Y, Fu J, Li X, Yang J, Jiang M, Ding K, et al. A minor (<50%) signet-ring cell component associated with poor prognosis in colorectal cancer patients: a 26-year retrospective study in China. PLoS One 2015; 10: e0121944.
17. Raab HR. Die R1-Resektion beim Rektumkarzinom [R1 resection in rectal cancer]. Chirurg 2017; 88: 771-6.
18. Sung S, Kim SH, Lee JH, Nam TK, Jeong S, Jang HS, et al. Continuous Effect of Radial Resection Margin on Recurrence and Survival in Rectal Cancer Patients Who Receive Preoperative Chemoradiation and Curative Surgery: A Multicenter Retrospective Analysis. Int J Radiat Oncol Biol Phys 2017; 98: 647-53.
19. Huh JW, Lee JH, Kim HR, Kim YJ. Prognostic significance of lymphovascular or perineural invasion in patients with locally advanced colorectal cancer. Am J Surg 2013; 206: 758-63.
20. Song JH, Yu M, Kang KM, Lee JH, Kim SH, Nam TK, et al. Significance of perineural and lymphovascular invasion in locally advanced rectal cancer treated by preoperative chemoradiotherapy and radical surgery: Can perineural invasion be an indication of adjuvant chemotherapy? Radiother Oncol 2019; 133: 125-31.
21. Long P, Zang Y, Wang H, Liang X, Xie X, Han Z, et al. Prognostic Nomogram for Patients with Radical Surgery for Non-Metastatic Colorectal Cancer Incorporating Hematological Biomarkers and Clinical Characteristics. Onco Targets Ther 2020 ;13: 2093-102.
22. Li Q, Zhuo C, Cai G, Li D, Liang L, Cai S. Increased number of negative lymph nodes is associated with improved cancer specific survival in pathological IIIB and IIIC rectal cancer treated with preoperative radiotherapy. Oncotarget 2014; 5: 12459-71.
23. Jia J, Zheng X, Chen Y, Wang L, Lin L, Ye X, et al. Stage-dependent changes of preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in colorectal cancer. Tumour Biol 2015; 36: 9319-25.
24. Ying HQ, Deng QW, He BS, Pan YQ, Wang F, Sun HL, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol 2014; 31: 305.

25. Zou Z, Liu H, Ning N, Li S, Du X, Li R. Clinical significance of pre-operative neutrophil lymphocyte ratio and platelet lymphocyte ratio as prognostic factors for patients with colorectal cancer. Oncology Letters 2016; 11: 2241-8.

26. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 2012; 17: 216-22.

27. Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE. Platelets in tumor progression: A host factor that offers multiple potential targets in the treatment of cancer. J Cell Physiol 2014; 229: 1005-15.

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# Effects of the Variants of Activin Receptor-like Kinase-1 and 2 on the Lipid Profile of Patients with Coronary Heart Disease

## Aktivin-benzeri Kinaz Reseptörleri-1 ve 2 Varyantlarının Koroner Arter Hastalarında Lipid Profiline olan Etkilerinin Araştırılması

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## ABSTRACT

**Introduction:** Coronary heart disease (CHD) due to atherosclerosis is a multifactorial disease with high morbidity caused by interaction of various genetic and environmental factors. Hyperlipidemia which is accepted as the most important risk factor for atherosclerosis; characterized by high concentration of low density lipoprotein (LDL) -cholesterol (LDL-C) and low concentration of high density lipoprotein (HDL)-cholesterol (HDL-C). Epidemiological studies prove the inverse relationship between HDL-C levels and CHD. Apolipoprotein A1, the major protein of HDL, is secreted as proprotein and then cleaved by C-terminal procollagen endoproteinase/bone morphogenetic protein-1 (BMP-1). Reporting of the role of BMP receptors in lipoprotein metabolism indicates that variations in these genes may be important. However, there are no studies in the literature about the variations in type I receptors for activin receptor-like kinase (ALK) 1 and ALK2 and its effects on lipid profile. In this study, it was aimed to determine the role of the gene variants of ALK1 (Q292P ve S333G) and ALK2 (R206H) receptors in the development of CHD and their effects on serum lipoprotein levels.

**Methods:** This study was carried out using a sample of 131 patients with CHD and 51 controls. ALK1 and ALK2 genotypes were determined by real-time polymerase chain reaction and technique.

**Results:** Genotype distributions of ALK1 and ALK2 were the same between the study groups ($p>0.05$). Mutations in ALK1 and ALK2 were observed only in the patient group. ALK1 Q292P mutation and ALK2 R206H mutation exerted positive effects on the serum lipid profile.

**Conclusion:** The findings of our study suggested that mutations of *ALK1* and *ALK2* genes may contribute to antiatherogenic lipid profile and may protect against the development of CHD.

**Keywords:** Mutation, coronary hearth disease, ALK1, ALK2

## ÖZ

**Amaç:** Aterosklerozdan kaynaklanan koroner kalp hastalığı (KKH) çeşitli genetik ve çevresel etmenlerin etkileşimden kaynaklanan morbimortalitesi yüksek multifaktöriyel bir hastalıktır. Ateroskleroz için en önemli risk faktörü kabul edilen hiperlipidemi; düşük yoğunluklu lipoprotein (LDL)-kolesterolün (LDL-K) yüksek konsantrasyonu ve yüksek yoğunluklu lipoprotein (HDL)-kolesterolün (HDL-K) düşük konsantrasyonu ile karakterizedir. Epidemiyolojik çalışmalar HDL-K seviyeleri ve KKH arasındaki ters ilişkiyi kanıtlamaktadır. HDL'nin başlıca proteini olan Apolipoprotein A1, proprotein olarak sekrete edilir ve sonra C-terminal prokollajen endoproteinaz/kemik morfogenezi ile ilişkili protein-1 (BMP-1) tarafından kesilir. BMP reseptörlerinin lipoprotein metabolizmasındaki görevlerinin bildirilmesi bu genlerdeki varyasyonların önemli olabileceğine işaret etmektedir. Ancak tipI reseptör aktivin reseptörü benzeri kinaz (ALK) 1 ve ALK2'ye ait varyasyonlar ve lipid profil'ine olan etkileri ile ilgili literatürde çalışma bulunmamaktadır. Biz çalışmamızda ALK2'ye ait R206H, ALK1 Q292P ve S333G gen varyantlarının KKH ile ilişkini ve lipoprotein metabolizması üzerine olan etkilerinin incelenmesini amaçladık.

**Yöntemler:** Çalışma gruplarımız 131 KKH ve 51 erkek kontrolden oluşmuştur. ALK1 ve ALK2 genotipleri gerçek zamanlı polimeraz zincir reaksiyonu ile belirlenmiştir.

**Bulgular:** ALK1 ve ALK2 genotip dağılımları çalışma gruplarında benzer gözlenmiştir. Ancak ALK1 ve ALK2 mutasyonları sadece hasta grubunda bulunmuştur. ALK1 Q292P mutasyonu ile ALK2 R206H mutasyonunun serum lipid profiline olumlu katkısını gözlemledik.

**Sonuç:** Çalışmamızın bulguları *ALK1* ve *ALK2* genlerine ait mutasyonların antiaterojenik lipid profiline katkı sağlayabileceği ve bu şekilde KKH gelişiminde koruyucu olabilecekleri izlenimini vermiştir.

**Anahtar Kelimeler:** Mutasyon, koroner kalp hastalığı, ALK1, ALK2

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## Introduction

Atherosclerosis is a progressive and degenerative disease, usually beginning in childhood, showing clinical symptoms in middle age, caused by genetic and environmental factors, normal and modified lipoproteins, monocytes, macrophage foam cells, T lymphocytes, endothelial cells (ECs), smooth muscle cells and fibroblasts complex interactions (1). Coronary heart disease (CHD), which develops as a result of atherosclerosis, still remains a serious cause of death in the world, is responsible for about 50% of deaths in the United States and Europe and 34% in Turkey.

Bone morphogenetic protein (BMP) is a metalloproteinase belonging to the growth factor transducer beta (TGF-β) superfamily. They were first identified as factors that caused the formation of bone and cartilage. However, it was later determined that they also showed broad spectrum biological activities in different tissues including blood vessels, heart, kidney, neurons, liver and lung. Studies have shown that BMPs can also form osteal tissue in "extraosteal" organs, making this protein a candidate for atherosclerosis. Indeed, recent research has shown that BMP ligands increase in vascular calcific lesions associated with atherosclerosis, diabetes and chronic renal failure (2-9). BMPs transmit their signals through two types of receptors, type I and type II. Type I receptors are essential for signaling. Type II receptors are responsible for binding to ligands and expression of type I receptors. Type II receptors phosphorylate type I receptors in the stable complex formed by type I and type II receptors following ligand binding.

The type I receptor "activin receptor-like kinase (ALK1)" plays an active role in EC biology. ALK1 has often been studied in relation to angiogenesis. However, the demonstration that ALK1 is expressed in atherosclerotic lesions suggests that it also plays a role in atherogenesis (10). In addition, Kraehling and colleagues reported in their study that ALK1 is a new low-affinity, high-capacity receptor for low density lipoprotein (LDL) in ECs that functions during hypercholesterolemia and supports LDL transcytosis. The determination of direct binding of ALK1 to LDL, unlike lipoprotein receptor (LDLR), and the lack of down-regulation of this binding by sterols and Proprotein convertase subtilisin/kexin type 9 have made ALK1 a new beacon of hope for the treatment of atherosclerosis (11).

The type I activin A receptor, also known as ALK2, is a transmembrane serine/threonine kinase receptor and following BMP binding activates intracellular signaling pathways via Smad1/5, Erk1/2 and p38. The ALK2 receptor, showing more limited signal specificity, is sensitive to BMP-5-6-7 signals. *ALK2* gene mutations cause the activation of BMP-specific intracellular signals without ligand binding to the receptor. In addition, the reporting that ALK1 expression is dependent on high density lipoprotein (HDL) induction to ALK2 indicates that variations in this gene may be important (12). Recent studies have shown evidence of the role of BMPs and their receptors in atherosclerosis (8,10,12,13).

Considering this information, it is worth studying the variations of BMP receptors as new biological markers that may cause individual differences in the treatment of atherosclerosis, which is a very serious health problem.

In our study, we aimed to investigate the effects of R206h, ALK-1 Q292P and s333g missense mutations of ALK2 induced by HDL with antiatherogenic properties due to its role in reverse cholesterol transport on CHD development and lipoprotein metabolism.

## Methods

For the analysis of the mutations identified in our study, the cases were included in the study based on the clinical criteria determined below, DNA belonging to these samples was prepared and purity determination was made and DNA levels were calculated and stored at +4°C until the time of the study. In addition, after all individuals in the study groups were informed, informed consent form was obtained and they were included in the study. Our study was carried out by the ethics committee decision numbered 2010/702-194 taken from İstanbul University Faculty of Medicine Clinical Research Ethics Committee and was supported by İstanbul University Scientific Research Projects Unit (no: 11304).

R206H (rs number: 121912678) ALK-1 q292p and s333g of ALK2 were studied using real - time polymerase chain reaction method and enzyme-linked immunosorbent assay technique to determine serum apoprotein A1 level in the obtained DNA samples. The distribution of genotypes and alleles in patient and control groups was analyzed by statistical analysis and it was attempted to determine whether they posed a risk in disease development. In addition, as related to CHD risk factors, body mass index (BMI) ($kg/m^2$), arterial hypertension (≥140 mmHg systolic blood pressure of ≥90 mmHg diastolic blood pressure), hyperlipidemia (total cholesterol >240 mg/dL and cholesterol >250 mg/dL) were evaluated.

Two sample groups were used in this study.

In the first group, 138 angiography (-) male individuals were enrolled in the control group. Participants in the control group were not taking drugs with known effects on serum lipid levels during sample extraction (lipid-lowering drugs such as statins or fibrates, beta-blockers, diuretics or hormones).

The second group was made up of 131 male patients with angiography (+) diagnosed with CHD by coronary angiography method followed by the İstanbul University Department of Cardiology of the Faculty of Medicine. Six of the patients were on no medication, 1 was using phenofibrate and 124 were receiving statin treatment. And all but one of them were receiving antihypertensive treatment.

### Statistical Analysis

Statistical analysis of this study was conducted using SPSS 20 package program. The statistical significance limit was taken as $p<0.05$.

Whether the data belonging to the patient and control groups comply with the normal distribution was analyzed with the Kolmogorov-Smirnov test. Student's t-test was used to determine body mass indexes, and chi-square ($\chi^2$) and Fisher's exact tests were used to evaluate the differences between groups in the frequency of genotype and alleles. The Kruskal-Wallis method was used for comparing clinical and non-clinical parameters with alleles between the patient and control groups,

and ANOVA and Student's t-test was used to examine the genotype. Gene counting method was used in calculations of allele frequency.

## Results

Our study consisted of 131 CHD and 138 volunteer healthy controls followed at the İstanbul University Faculty of Medicine Department of Cardiology. The properties for the groups are given in Table 1. Accordingly, there were no statistically significant differences between the patient and the control group in terms of age, serum apoprotein A1, triglycerides, very-low-density lipoprotein (VLDL)-C, HDL-C and BMI values and alcohol consumption (p>0.05). Cigarette consumption was high in the patient group compared to the control group (63.8% in the patient group; 47% in the control group; p=0.006). Also in the patient group, systolic blood pressure (p≤0.001),diastolic blood pressure (p=0.008), total cholesterol (p ≤0.001), LDL-C (p≤0.001) of total cholesterol/HDL-C (p≤0.001),HDL-Cl/LDL-C (p=0.008) compared to the control group values were found to be low and statistically significant.

94.6% of the individuals in our patient group use statins, 0.76% use fenofibrate type drugs, and 4.5% do not receive antihyperlipidemic treatment. In addition, all but one of our patients have hypertension and use antihypertensive drugs. We attribute the lower serum lipid/lipoprotein and blood pressure values observed in the patient group compared to our control group to the use of medication.

The genotype and allele distributions of *ALK1* and *ALK2* gene mutations studied in patient and control groups are shown in Table 2. When ALK1 Q292P and S333G and ALK2 r206h genotype distributions were examined in study groups, no statistically significant differences were observed. However, mutant genotypes of *ALK1* and *ALK2* genes were observed only in the patient group and no mutations were found in the control group (Table 2).

When the effect of ALK1 Q292P mutations on serum Apoprotein A1, lipoprotein levels, BMI and blood pressures were examined, serum triglycerides (p=0.020), LDL-C (p=0.045) and VLDL-C (p=0.022) levels were significantly lower in the patients with mutant genotypes compared to those with no mutations. The effect of ALK1 S333g mutation on serum lipids, blood pressures and body mass index values was not observed (p>0.05) (Table 3).

When the effect of ALK2 r206h mutation on serum Apoprotein A1, lipoprotein levels, BMI and blood pressures were examined in the patient group, serum LDL-K (p=0.017) levels were significantly lower in individuals with mutant genotypes compared to non-mutant individuals (Table 4).

Since ALK1 and ALK2 variants were not found in the control group, we were unable to evaluate their effect on lipid profile, BMI and blood pressures.

**Table 1. Characteristics of the groups**

| | Groups | | p |
|---|---|---|---|
| | Control (n=138) | Patient (n=131) | |
| **Age (year)** | 50.91±7.46 | 50.25±4.65 | 0.393 |
| **Age of the first MI (year)** | - | 50.60±6.24 | - |
| **SBP (mmHg)** | 132.82±20.75 | 124.19±12.88 | **<0.001** |
| **DBP (mmHg)** | 78.94±15.75 | 74.80±8.53 | **0.008** |
| **BMI (kg/m²)** | 26.29±3.55 | 25.62±3.61 | 0.134 |
| **Apoprotein A-1** | 1.34±0.24 | 1.27±0.21 | 0.136 |
| **Total-C (mmol/ L)** | 5.16±1.27 | 4.45±1.10 | **<0.001** |
| **Triglyceride (mmol/L)** | 1.68±0.87 | 1.66±0.75 | 0.876 |
| **LDL-C (mmol/L)** | 3.24±0.84 | 2.72±0.90 | **<0.001** |
| **HDL-C (mmol/L)** | 1.05±0.29 | 1.06±0.25 | 0.808 |
| **VLDL-C (mmol/L)** | 0.77±0.37 | 0.71±0.26 | 0.151 |
| **Total-C/HDL C** | 5.28±1.96 | 4.39±1.35 | **<0.001** |
| **HDL-C/LDL-C** | 0.37±0.12 | 0.43±0.17 | **0.008** |
| **Smoking** | 47% | 63.8% | **0.006** |
| **Alcohol use** | 39.9% | 45% | 0.390 |
| **Presence of type-2 diabetes (%)** | - | 22.5% | - |
| **Presence of hypertension (%)** | - | 99.2% | - |
| **Stent presence /absence(%)** | - | 14.13/85.87 | - |
| **A vein (%)** | - | 82.27% | - |
| **Two veins (%)** | - | 15.18% | - |
| **Three veins (%)** | - | 2.53% | - |

The values of age, serum lipid, BMI and blood pressures in the table were given as X + Standard deviation, and other values as %. The degree of intergroup significance was examined by the student t-test, CHD: Coronary heart patients, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, N: sample number, LDL: low density lipoprotein, VLDL: very-low-density lipoprotein, HDL: high density lipoprotein, MI: myocardial infarction

**Table 2. Distribution of ALK1 and ALK2 genotypes in the groups**

| ALK1 and ALK2 mutations | Groups | | p |
|---|---|---|---|
| | Control (n=138) | CHD patients (n=131) | |
| **ALK1 Q292P genotypes** | | | |
| Normal | 138 (100%) | 127 (96.9%) | FE =0.055 |
| Mutant | - | 4 (3.1%) | |
| **ALK1 S333G genotypes** | | | |
| Normal | 138 (100%) | 127 (96.9%) | FE =0.055 |
| Mutant | - | 4 (3.1%) | |
| **ALK2 R206H genotypes** | | | |
| Normal | 138 (100%) | 128 (97.7%) | FE =0.114 |

The values in the table are given as sample number and percentage. The degree of intergroup significance was examined by the Student's t-test. CHD: Coronary heart disease, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, n: number of samples, FE: Fisher's exact test, ALK: activin receptor-like kinase

**Table 3. Effect of ALK1 Q292P and S333S mutations on serum lipid profile, blood pressures and body mass index in patient group**

| | ALK1 Q292p mutation | | |
|---|---|---|---|
| | Normal | Mutant | p |
| **Apoprotein-A1** | 1.28±0.21 | 1.10±1.17 | 0.165 |
| **Total-C (mmol/L)** | 4.48±1.11 | 3.76±0.77 | 0.160 |
| **Triglyceride (mmol/L)** | 1.68±0.76 | 1.15±0.27 | 0.020 |
| **HDL-C (mmol/L)** | 1.06±0.25 | 1.17±0.40 | 0.622 |
| **LDL-C (mmol/L)** | 2.74±0.90 | 2.14±0.38 | 0.045 |
| **VLDL-C (mmol/L)** | 0.72±0.26 | 0.52±0.10 | 0.022 |
| **BMI (kg/m$^2$)** | 25.60±3.65 | 26.24±1.99 | 0.581 |
| **SBP (mmHg)** | 124.25±12.94 | 122.50±12.58 | 0.790 |
| **DBP (mmHg)** | 74.88±8.62 | 72.50±5.00 | 0.419 |
| | **ALK1 S333G mutation** | | |
| | **Normal** | **Mutant** | **p** |
| **Apoprotein-A1** | 1.26±0.21 | 1.37±0.21 | 0.322 |
| **Total-cholesterol (mmol/L)** | 4.44±1.10 | 5.03±1.29 | 0.290 |
| **Triglyceride (mmol/L)** | 1.66±0.75 | 1.66±0.75 | 0.999 |
| **HDL-C(mmol/L)** | 1.06±0.25 | 1.06±0.23 | 0.983 |
| **LDL-C (mmol/L)** | 2.70±0.89 | 3.20±1.08 | 0.281 |
| **VLDL-C (mmol/L)** | 0.71±0.26 | 0.68±0.14 | 0.790 |
| **BMI (kg/m$^2$)** | 25.56±3.56 | 28.13±5.39 | 0.225 |
| **SBP (mmHg)** | 124.25±12.88 | 122.50±15.00 | 0.790 |
| **DBP(mmHg)** | 74.80±8.53 | 75.00±10.0 | 0.964 |

The values in the table are given as X + standard deviation. The degree of intergroup significance was examined by the student t-test. BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low density lipoprotein, VLDL: very-low-density lipoprotein, HDL: high density lipoprotein, ALK: activin receptor-like kinase

## Discussion

Atherosclerotic CHD is one of the greatest threats to Global Health (14). Atherosclerosis is a complex disease influenced by various environmental factors and accompanied by many genetic variations with low penetration (15). For CHD with high morbimortality (16) endothelial dysfunction, inflammation, abnormal lipoprotein and homocysteine metabolism are very important risk factors (17).

In recent studies, the presentation of evidence that BMPs and their receptors play a role in atherosclerosis has caused researchers to turn to these proteins. The results of our study published in 2018 show that the BMP1 5'UTR + 104 (T/C) variation may affect serum Apo A1 and lipoprotein levels due to statin therapy and thus contribute to the development of CHD (13). Studies of BMPs remain current and are continuing rapidly, but studies of BMP receptors that enable BMP signaling and their effects on atherosclerosis are limited. The variations in these proteins appear to be a very current and important issue, as they can affect the progressive aspect of atherosclerosis.

In our study, we studied the frequency of ALK1 type I receptors Q292p and S333G and ALK2 R206h mutations in CHD and their effects on lipoproteins. The relationship between ALK1 and ALK2 and CHD and the effect of these variants on lipoproteins has not been found in

**Table 4. Effect of ALK2 R206H mutation on serum lipid profile, blood pressures and body mass index in CHD patient group**

| | ALK2 R206H mutation | | |
|---|---|---|---|
| | CC | CT | p |
| Apoprotein-A1 | 1.28±0.21 | 1.11±1.16 | 0.201 |
| Total-C (mmol/L) | 4.48±1.10 | 3.43±0.53 | 0.066 |
| Triglyceride (mmol/L) | 1.67±0.76 | 1.56±1.16 | 0.408 |
| HDL-C (mmol/L) | 1.06±0.25 | 0.85±0.12 | 0.074 |
| LDL-C (mmol/L) | 2.74±0.90 | 1.97±0.26 | 0.017 |
| VLDL-C (mmol/L) | 0.71±0.26 | 0.69±0.08 | 0.751 |
| BMI (kg/m$^2$) | 25.66±3.63 | 23.96±1.56 | 0.190 |
| SBP (mmHg) | 124.14±12.51 | 126.66±28.86 | 0.894 |
| DBP (mmHg) | 74.92±8.51 | 70.00±10.00 | 0.325 |

The values in the table are given as X + standard deviation. The degree of intergroup significance was examined by the student t-test. BMI: Body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL: low density lipoprotein, VLDL: very-low-density lipoprotein, HDL: high density lipoprotein, ALK: activin receptor-like kinase
CHD: coronary heart disease

the literature. For this reason, we could not find the opportunity to compare our results. In general, mutations on ALK1 have been associated with the development of direct connections between arteries and vessels, or with hereditary hemorrhagic telangiectasia (HHT 2), which is autosomal dominant inheritance and systemic fibrovascular dysplasia, characterized by arteriovenous malformations (18-21). There are publications reporting that ALK-1 mutations are associated with pulmonary hypertension in HHT patients (22,23).

Studies pointing out the role of ALK1 in atherosclerosis have mainly drawn attention to TGF-family signaling, and according to independent study data, inhibition of BMP signal reduces the formation of atherosclerotic plaques (24,25). Although until recently there was little evidence of a link between ALK1 and atherosclerosis, an increase in ALK1 expression was also observed in atherosclerotic lesions, based on data from two studies in mice (26) and humans (10).

ALK1 has two independent roles in atherosclerosis through direct binding of LDL to extracellular domein to mediate LDL uptake and provide BMP signaling. In addition, Kraehling and colleagues (11) reported that ALK1 facilitates LDL uptake but does not target LDL for impairment, while LDLR and ALK1 overexpression increase fluorescence labeled LDL [dioctadecylindocarbocyanine (DiI)-LDL] uptake, they did not observe the effect of ALK2 overexpression on DiI-LDL uptake.

According to the results of our study, serum triglycerides, LDL-C and VLDL-C levels were statistically significantly lower in individuals with ALK1 Q292P mutant genotype than in non-mutant individuals. According to this data, it may be possible to say that ALK1 Q292P mutation shows antiatherogenic properties when its positive effect on lipid profile is evaluated.

ALK2 enables the rearrangement of ALK1. However, gene deletion experiments produce different phenotypes, indicating that the respective target genes of ALK1 and ALK2 are different. ALK1 deficiency is associated with HHT and the formation of arteriovenous malformations, while ALK2 affects the development of cardiac output pathway and aortic derivatives. A high level of ALK2 relative to ALK3 and ALK6 may alter the inflammatory effects of BMP-2/4 in the endothelium (12).

Yao et al. (24) showed that HDL promotes ALK2 expression in ECs, which allows induction of ALK-1, vascular endothelial growth factor (VEGF) and matrix Gla protein (MGP). These investigators showed that the HDL induction of ALK2 is dependent on the BMP signal and also affects the correlation of a repressive homeodomain protein (Msh homeobox2) MSX2 and the activating homeodomain proteins DLX3 and DLX5 (homeobox protein) with the *ALK2* gene. The significance of these findings is confirmed in apoA1 transgenic mice with high HDL levels and resistant to atherogenesis. Mice mentioned show similar changes in aortic gene expression as seen in *in vitro* ECs. In this way, HDL protects the arterial wall by increasing the BMP response system, which allows the increase of VEGF, essential for endothelial survival, and the increase of MGP, which prevents excessive BMP activity and vascular calcification.

According to the results of our study, LDL-C levels were statistically significantly lower in individuals with ALK2 R206h mutant genotype than in non-mutant individuals. According to this data, it may be possible to say that ALK2 R206h mutation shows antiatherogenic properties when its positive effect on lipid profile is evaluated.

## Conclusion

We observed ALK1 Q292P and S333G and ALK2 R206h mutations in our study, albeit with a low frequency, only in the patient group. We didn't find any mutations in the control group. Therefore, we were unable to assess the effect of these mutations on control group characteristics. However, we observed the positive contribution of the ALK1 Q292P mutation and the ALK2 R206H mutation to the serum lipid profile in the patient group. The findings of our study suggest that mutations in the *ALK1* and *ALK2* genes, which are BMP receptors, may contribute to the antiatherogenic lipid profile and thus be protective in the development of CHD. We believe that the interaction of BMP protein and signaling pathway variants with serum lipids deserves a better understanding by continuing our study in the study group with a larger sample.

### Ethics

**Ethics Committee Approval:** Our study was carried out by the ethics committee decision numbered 2010/702-194 taken from İstanbul University Faculty of Medicine Clinical Research Ethics Committee and

was supported by İstanbul University Scientific Research Projects Unit (no: 11304).

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

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

**Authorship Contributions:** Design - A.B.A.T., H.Y.A.; Data Collection or Processing - A.B.A.T., E.T.; Analysis or Interpretation - A.B.A.T., H.Y.A.; Literature Search - A.B.A.T., H.Y.A.; Writing - A.B.A.T.

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## References

1. Page IH. Atherosclerosis; an introduction. Circulation 1954; 10: 1-27.
2. Zhang M, Sara JD, Wang FL, Liu LP, Su LX, Zhe J, et al. Increased plasma bmp-2 levels are associated with atherosclerosis burden and coronary calcification in type 2 diabetic patients. Cardiovasc Diabetol 2015; 14: 64.
3. Chang K, Weiss D, Suo J, Vega JD, Giddens D, Taylor WR et al. Bone morphogenic protein antagonists are coexpressed with bone morphogenic protein 4 in endothelial cells exposed to unstable flow in vitro in mouse aortas and in human coronary arteries: role of bone morphogenic protein antagonists in inflammation and atherosclerosis. Circulation 2007; 116: 1258-66.
4. Yung LM, Sánchez-Duffhues G, Ten Dijke P, Yu PB. Bone morphogenetic protein 6 and oxidized low-density lipoprotein synergistically recruit osteogenic differentiation in endothelial cells. Cardiovasc Res 2015; 108: 278-87.
5. Csiszar A, Ahmad M, Smith KE, Labinskyy N, Gao Q, Kaley G, et al. Bone morphogenetic protein-2 induces proinflammatory endothelial phenotype. Am J Pathol 2006; 168: 629-38.
6. Csiszar A, Labinskyy N, Jo H, Ballabh P, Ungvari Z. Differential proinflammatory and prooxidant effects of bone morphogenetic protein-4 in coronary and pulmonary arterial endothelial cells. Am J Physiol Heart Circ Physiol 2008; 295: H569-77.
7. Li X, Yang HY, Giachelli CM. BMP-2 promotes phosphate uptake, phenotypic modulation, and calcification of human vascular smooth muscle cells. Atherosclerosis 2008; 199: 271-7 .
8. Nakagawa Y, Ikeda K, Akakabe Y, Koide M, Uraoka M, Yutaka KT, et al. Paracrine osteogenic signals via bone morphogenetic protein-2 accelerate the atherosclerotic intimal calcification in vivo. Arterioscler Thromb Vasc Biol 2010; 30: 1908-15.
9. Buendía P, de Oca AM, Madueño JA, Merino A, Martín-Malo A, Aljama P, et al. Endothelial microparticles mediate inflammation-induced vascular calcification. FASEB J 2015; 29: 173-181.
10. Yao Y, Zebboudj AF, Torres A, Shao E, Bostrom K. Activin-like kinase receptor 1 (ALK1) in atherosclerotic lesions and vascular mesenchymal cells. Cardiovasc Res 2007; 74 :279-89.
11. Kraehling JR, Chidlow JH, Rajagopal C, Sugiyama MG, Fowler JW, Lee MY, et al. Genome-wide rnai screen reveals alk1 mediates ldl uptake and transcytosis in endothelial cells Nat Commun 2016; 7: 13516.
12. Yao Y, Shao ES, Jumabay M, Shahbazian A, Ji S, Kristina I. Boström. High density lipoproteins affect endothelial bmp-signaling by modulating expression of the activin-like kinase receptor 1 and 2. Arterioscler Thromb Vasc Biol 2008; 28: 2266-74.
13. Akadam Teker B, Ozkara G, Kurnaz Gomleksiz O, Bugra Z, Teker E, Ozturk O, et al. BMP1 5'UTR+104 T/C gene variation: can be a predictive marker for serum HDL and apoprotein A1 levels in male patients with coronary heart disease. Mol Biol Rep 2018; 45: 1269-76.
14. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American heart association. Circulation 2017; 135: e146-e603.
15. Liu L, Li Y, Tollefsbol TO. gene-environment interactions and epigenetic basis of human diseases. Curr Issues mol biol 2008; 10: 25-36.
16. Raposo M, Sousa P, Nemeth S, Couto A, Santos M, Pinheiro J, et al. Polymorphism in cardiovascular diseases (cvd) susceptibility loci in the azores islands (portugal) Open j genet 2011; 1: 48-53.
17. Roy H, Bhardwaj S, Yla-Herttuala S. Molecular Genetics of atherosclerosis. Hum Genet 2009: 467-91.
18. Guttmacher AE, Marchuk DA, White RI Jr. Hereditary haemorrhagic telangiectasia. N Engl J Med 1995; 333: 918-24.
19. Johnson DW, Berg JN, Baldwin MA, Gallione CJ, Marondel I, Yoon SJ, et al. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat Genet 1996; 13: 189-95.
20. Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary haemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 1989; 32: 291-7.
21. Vincent P, Plauchu H, Hazan J, Faure S, Weissenbach J, Godet J. A third locus for hereditary haemorrhagic telangiectasia maps to chromosome 12q. Hum Mol Genet 1995; 4: 945-9.
22. Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, Winship I, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 2001; 345: 325-34.
23. Selva-O'Callaghan A, Balada E, Serrano-Acedo S, Aznar CPS, Ordi-Ros J. Mutations of activin-receptor-like kinase 1 (ALK-1) are not found in patients with pulmonary hypertension and underlying connective tissue disease. Clin Rheumatol 2007; 26: 947-9.
24. Yao Y, Bennett B, Wang X, Rosenfeld ME, Giachelli C, Luis AJ, et al. Inhibition of bone morphogenetic proteins protects against atherosclerosis and vascular calcification. Circ Res 2010; 107: 485-94.
25. Derwall M, Malhotra R, Lai CS, Beppu Y, Aikawa E, Seehra JS, et al. Inhibition of bone morphogenetic protein signaling reduces vascular calcification and atherosclerosis. Arterioscler Thromb Vasc Biol 2012; 32: 613-22.
26. Korff T, Aufgebauer K, Hecker M. Cyclic stretch controls the expression of CD40 in endothelial cells by changing their transforming growth factor-beta1 response. Circulation 2007; 116: 2288-97.

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# Effects of Anaemia Parameters on Metabolic Control in Children with Type-1 Diabetes Mellitus

## Tip-1 Diabetes Mellituslu Çocuklarda Anemi Parametrelerinin Metabolik Kontrol Üzerine Etkisi

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## ABSTRACT

**Introduction:** Anaemia parameters in children with type-1 diabetes and their relationship with metabolic control has received little attention in the literature. We aimed to determine the incidence of anaemia and to investigate anaemia parameters and their relationship with metabolic control in paediatric type-1 diabetes mellitus (DM) patients.

**Methods:** A retrospective case control study was conducted using the medical records of 33 patients with type-1 diabetes and 33 healthy children. In both groups, anaemia parameters including haemogram parameters and iron, total iron-binding capacity (TIBC), ferritin, vitamin B12 and folate were noted. In the case group, HbA1c levels, duration of diabetes and insulin treatment dose were also noted.

**Results:** Mean diabetes duration was 8.4±11.4 months, mean HbA1c level was 10.6±2.9 and mean insulin treatment dose was 0.7±0.2 u/kg/day. Comparison of haemogram parameters between the case and control groups were non-significant. TIBC was lower in the patients than in controls. Folate and ferritin were higher in patients than in controls.

**Conclusion:** According to this study, type-1 DM did not increase the risk for anaemia in children. Ferritin was higher in patients than in controls, which suggests that inflammation was present in the patients with type-1 DM.

**Keywords:** Anaemia, type-1, diabetes mellitus, HbA1c, insulin, children

## ÖZ

**Amaç:** Tip-1 diyabetli çocuklarda anemi parametrelerinin metabolik kontrolle ilişkisi literatürde az yer almaktadır. Tip-1 diabetes mellitus (DM) tanılı çocuklarda anemi insidansı, anemi parametreleri ve bu parametrelerin metabolik kontrolle ilişkisinin araştırılması planlanmıştır.

**Yöntemler:** Benzer yaş ve cinsiyette olan 33 tip-1 diyabetli ve 33 sağlıklı çocuğun tıbbi kayıtlarından retrospektif olgu kontrol çalışması yapılmıştır. Her iki grupta hemogram parametreleri ve demir, total demir bağlama kapasitesi (TDBK), ferritin, vitamin B12, folat anemi parametreleri olarak kayıt edildi. Ayrıca olgu grubunda HbA1c seviyeleri, diyabet süresi ve insülin tedavi dozu not edildi.

**Bulgular:** Tip-1 DM'li çocuklarda diyabet süresi 8,4±11,4 ay, HbA1c seviyesi 10,6±2,9 ve insülin tedavi dozu 0,7±0,2 u/kg/gündü. Olgu ve kontrol grubunda hemogram parametrelerinin karşılaştırılmasında anlamlı fark saptanmadı. TDBK kontrol grubuna göre daha düşük saptandı (p=0,02). Folat ve ferritin seviyesi hastalarda kontrol grubuna göre daha yüksek saptandı (p=0,001).

**Sonuç:** Bu çalışmaya göre tip-1 DM çocuklarda anemi riskini artırmamaktadır. Hastalarda ferritin seviyesi kontrole göre daha yüksek saptanmıştır, bu durum tip-1 DM'de enflamasyonun varlığını desteklemektedir.

**Anahtar Kelimeler:** Anemi, tip-1, diabetes mellitus, HbA1c, insülin, çocuk

## Introduction

Type-1 diabetes mellitus (DM) is one of the most common chronic childhood diseases and its incidence has doubled during the last decade. In some studies, due to the chronic inflammatory state of type-1 DM, it was considered that children may be at a higher risk of developing anaemia, which may contribute to disease complications (1,2). Anaemia in type-1 DM may have a multifactorial background; specifically, it may be associated a more rapid erythrocyte turnover leading to higher HbA1c (3). Other autoimmune diseases (thyroiditis, celiac disease, Addison's disease and atrophic gastritis) may be accompanied by type1 DM and can lead to anaemia. Some studies showed that the most common causes of anaemia in children with type-1 DM is iron deficiency (4,5). Iron deficiency in adults with type-1 DM is associated with prolonged illness and kidney malfunction (6,7).

In the present study, we aimed to assess the haemogram and iron metabolism parameters, as well as vitamin B12 and folate levels in

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children with type-1 DM. These results were then compared with those obtained from a group of healthy children to estimate the relation between type-1 DM and metabolic factors such as disease duration, insulin treatment dose and HbA1c levels.

## Methods

### Subjects

This study was a case control study at the paediatric clinic of Haseki Training and Research Hospital. A total of 66 children were recruited into the study: 33 with type-1 DM and 33 healthy children as a control group. Blood samples were collected during the routine control visit in the outpatient clinic. The patients were diagnosed according to the criteria established by the American Diabetes Association (8). Exclusion criteria were as follows: other autoimmune diseases (celiac, thyroiditis), abnormal renal/hepatic biochemical values, macrovascular complications and infections. Patients with haemoglobinopathies were also excluded from the study. Children enrolled for this study, according to their medical records, did not have chronic diabetes complications. The control group consisted of healthy children having similar characteristics with the patient group in terms of gender and age. They had visited the clinic for routine medical examination and were not diagnosed with any kind of disease. None of the participants had a history of iron supplementation or blood transfusion in the last six months.

In both groups, haemogram parameters including red blood cells, haemoglobin (HGB), haematocrit, mean corpuscular volume, mean corpuscular HGB and anaemia parameters including iron, iron-binding capacity, ferritin, vitamin B12 and folate were noted. In the case group, HbA1c levels, duration of diabetes and insulin subcutaneous treatment dose (insulin/kg/day) were noted. The reference ranges were as follows: HGB <12 gr/dL for the diagnosis of anaemia and red cell distribution width (RDW) >14, serum iron <30 µg/dL, total serum iron-binding capacity >350 µg/dL and ferritin <16 ng/mL for the diagnosis of iron deficiency anaemia.

### Ethics Statement

Informed consent forms were completed by all the participants. The study protocol was approved by the Ethics Committee of Haseki Training and Research Hospital (protocol number: 79-02/05/2014) and the study was performed in accordance with the Declaration of Helsinki.

### Biochemical Analysis

Blood samples were collected (without stasis after morning fasting) from all the participants. Serum samples placed into tubes with gel were allowed to clot before centrifugation. Following centrifugation for 10 min at 1000 g, the serum was aliquoted and kept at -70°C until the day of the study.

The samples for haemogram were moved into tubes containing K2EDTA (Becton Dickinson, UK) and the analysis was performed using an LH 780 (Beckman Coulter, USA) fully automated haematology system. HbA1c was measured using a turbidimetric inhibition immunoassay with VARIANT II autoanalyser, for which 4.8%-6% were within normal ranges and higher levels were considered significant. Serum iron levels and total iron-binding capacity (TIBC) were measured using the calorimetric method and a Cobas Integra 800 analyzer Roche, Mannheim, Germany). Ferritin, folate and vitamin B12 levels were determined via chemiluminescence immunoassays and an autoanalyser (Elecsys E170, Japan).

### Statistical Analysis

SPSS version 15.0 was used for data analysis. For the comparison of the two groups, Student's t-test was used when the numerical variables were in the normal ranges and Mann-Whitney U test was used for those in abnormal ranges. Categorical variable ratios between the groups were analysed with the chi-square test. Correlations between the numerical variables were assessed by Spearman's correlation analysis. A p-value of $<0.05$ was considered statistically significant.

## Results

Among the 33 children in the case group, 18 were males (54.5%) and 15 were females (45.5%); in the control group, 18 children were males (54.5%) and 15 were females (45.5%). The mean age of the case group was 12.5±3.8 years and that of the control group was 12.3±2.6 years. There was no statistically significant difference between the groups in terms of age or gender. In the case group, the duration of diabetes was 0-42 months (8.4±11.4 months), HbA1c levels were 10.6±2.9 and insulin treatment doses were 0.7±0.2 u/kg/day (Table 1).

Comparison of the haemogram parameters of the patient and control groups were non-significant, but both ferritin and folate concentrations increased significantly in the case group (p=0.001) and the TIBC was significantly decreased (p=0.022) (Table 2). Comparison of the laboratory parameters in type-1 DM patients according to the duration of DM was not significant between ≤12 months and >12 months.

According to the HGB levels, the case group was divided into two groups: >12 gr/dL and <12 gr/dL. There was no significant between these groups in terms of age, gender, duration of diabetes, HbA1c and insulin treatment dose.

In the case group, correlations of haemogram and anaemia parameters with duration of diabetes were not significant. In addition, correlations of insulin treatment dose with haemogram-anaemia parameters were not significant. Correlations of HbA1c and anaemia-haemogram parameters were not significant, but there was a significant negative correlation of serum folate concentration with HbA1c (Table 3).

**Table 1. The demographic features and clinical findings of the patients with type-1 DM and healthy control**

| Parameters | DM type-1 (n=33) | Controls (n=33) | p |
|---|---|---|---|
| Age (years) | 12.5±3.8 (4-18) | 12.3±2.6 (7-17) | 0.597 |
| Gender (females, %) | 15 (45.5) | 15 (45.5) | 1.000 |
| Duration of diabetes (month) | 8.4±11.4 (0-42) | - | - |
| Insulin (U/kg/day) | 0.7±0.2 (0.4-1.3) | - | - |
| HbA1c (%) | 10.6±2.9 (6.5-18.6) | - | - |

DM: Diabetes mellitus

**Table 2. Comparison of laboratory parameters between the patients and controls**

| Parameters | DM type-1 (n=33) | Controls (n=33) | p |
|---|---|---|---|
| Haemoglobin (g/dL) | 13.3±1.9 (8.8-16.8) | 13.6±0.9 (12.5-15.6) | 0.372 |
| Haemoglobin (<12 g/dL) | 4 (12.1) | 0 (0.0) | 0.114 |
| Haematocrit (%) | 40.6±5.1 (31.3-51) | 40.2±2.1 (36.1-44.3) | 0.644 |
| MCV (fl) | 82.4±7.7 (59-98.6) | 83±3.8 (71-91) | 0.728 |
| RDW (%) | 14.4±2.2 (11.7-19.6) | 14.3±1.2 (12.4-17.8) | 0.577 |
| MCH (pg) | 27.2±3.2 (16.3-33.1) | 27.8±2.5 (20.9-33.3) | 0.520 |
| Vitamin B12 (pg/mL) | 303.2±178.4 (107-797) | 222.6±85.5 (98-407) | 0.092 |
| Folate (ng/mL) | 12.1±5 (3.4-24) | 8.7±3.1 (3.1-17.3) | 0.001 |
| Iron (µmol/L) | 79.6±44.5 (10.9-186) | 71.1±30.9 (3-130) | 0.375 |
| TIBC (µmol/L) | 329.2±55.9 (248-461) | 355.6±32.5 (254-412) | 0.022 |
| Ferritin (µg/L) | 53±34.2 (2.6-139) | 30.3±30.8 (5.3-156.1) | **0.001** |

TIBC: Total iron-binding capacity, DM: diabetes mellitus, MCV: mean corpuscular volume, RDW: red cell distribution width, MCH: mean corpuscular hemoglobin

**Table 3. Correlation of metabolic parameters in diabetes mellitus type-1 patients with anaemia-haemogram parameters**

| | | Duration of DM | Insulin U/kg/day | HbA1c |
|---|---|---|---|---|
| **Haemoglobin** | rho | -0.217 | 0.012 | 0.246 |
| | p | 0.224 | 0.947 | 0.168 |
| **Haematocrit** | rho | -0.233 | 0.001 | 0.304 |
| | p | 0.192 | 0.995 | 0.085 |
| **MCV** | rho | -0.110 | 0.192 | 0.021 |
| | p | 0.544 | 0.285 | 0.907 |
| **RDW** | rho | -0.017 | -0.185 | 0.075 |
| | p | 0.924 | 0.303 | 0.676 |
| **MCH** | rho | -0.103 | 0.204 | -0.049 |
| | p | 0.567 | 0.254 | 0.786 |
| **Vitamin B12** | rho | 0.142 | 0.175 | 0.035 |
| | p | 0.429 | 0.329 | 0.847 |
| **Folate** | rho | -0.047 | -0.042 | -0.345 |
| | p | 0.794 | 0.816 | 0.049 |
| **Iron** | rho | -0.124 | 0.204 | -0.118 |
| | p | 0.491 | 0.254 | 0.512 |
| **TIBC** | rho | 0.180 | -0.101 | -0.233 |
| | p | 0.317 | 0.576 | 0.191 |
| **Ferritin** | rho | -0.327 | -0.208 | 0.206 |
| | p | 0.063 | 0.247 | 0.250 |

TIBC: Total iron-binding capacity, DM: diabetes mellitus, MCV: mean corpuscular volume, RDW: red cell distribution width, MCH: mean corpuscular hemoglobin, rho: Spearman's rank correlation coefficient

## Discussion

To date, few studies have assessed the prevalence of anaemia among children with type-1 DM and its effects on metabolic control. In some studies, patients with type-2 diabetes and anaemia, usually accompanied by renal complications, were available (6,7). In the paediatric population, disturbances of renal function are rare. Therefore, anaemia among children with type-1 DM and its causes are controversial.

We found that only 4/33 (12.1%) patients had anaemia in the case group, which were caused by iron deficiency and there was no statistically significant difference between the groups (p=0.114). Similarly, Akkermans et al. (1) found lower prevalence rates of anaemia among children with type-1 DM. Specifically, they performed a two-centre prospective observational study in which the iron statuses of 227 children with type-1 DM were investigated. Their results indicated that iron deficiency anaemia prevalence was 3.1% and chronic disease prevalence was 3.7%. The deprived iron status was observed in 113 (50%) of the 227 children. In the study of Rusak et al. (9), none of the children with type-1 DM had anaemia. Although it is suggested that children with type-1 DM may be at a higher risk for anaemia, studies on this subject are rare. In an analysis of 200 Egyptian children with type-1 DM, anaemia was diagnosed in 37% of the patients and anaemia developed as a consequence of parasitic infestations and a lower socioeconomic situation (5).

In our patients, iron metabolism parameters and vitamin B12 levels were within the normal ranges, but the comparison of the case and control groups indicated that ferritin and folate concentration were higher and TIBC was lower in the case group. Normal vitamin B12 and iron concentrations in children with type-1 DM were also described by other authors (10). Normal iron status, B12 levels and high folic acid may be the result of regular controls and healthy nutrition. Higher ferritin and lower TIBC may be markers of inflammation (11). It is known that type-1 DM is an inflammatory disease. Rusak et al. (9) studied the markers of anaemia in children with type-1 DM and found significantly higher RDW, hepcidin which is a marker of inflammation, anaemia and vitamin B12 concentrations and lower TIBC.

In children with type-1 DM, knowledge about the impact of anaemia on HbA1c levels is rare and the results are conflicting. In some studies, the iron statuses of children and their potential impact on HbA1c levels were studied. Results indicated that decreased iron levels might lead to increased HbA1c levels. (12-14). Tarim et al. (4) and Salah et al. (5) reported elevated HbA1c levels in type1 DM patients with iron deficiency anaemia. They described a significant decrease in HbA1c levels after iron replacement therapy in patients with iron deficiency anaemia. In contrast with several previous studies, our results suggest that anaemia

and haemogram parameters have no effect on HbA1c concentrations. A previously mentioned report from Akkerman et al. (1) also found that HbA1c levels were not associated with iron deficiency.

In this study, haemogram parameters, TIBC, serum iron and vitamin B12 and ferritin levels did not show a relationship with duration of diabetes, HbA1c, or daily insulin dosage. However, there was a significant negative correlation with HbA1c and serum folate concentrations. It is considered that folate deficiency in children with type-1 DM might affect metabolic control. Therefore, additional studies to assess the relationship between folate concentration and HbA1c are needed.

Our study had an advantage over previous studies because we evaluated anaemia-haemogram parameters and their association with metabolic parameters, including insulin treatment dose, duration of diabetes and HbA1c. However, our results were limited by a small sample size.

## Conclusion

The present study confirms that metabolic control parameters are not associated with haemogram and anaemia parameters in children with type-1 DM. Nevertheless, additional studies with larger sample sizes are recommended.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Ethics Committee of Haseki Training and Research Hospital (protocol number: 79-02/05/2014) and the study was performed in accordance with the Declaration of Helsinki. **Informed Consent:** Informed consent forms were completed by all the participants.

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

**Authorship Contributions:** Concept- S.A.; Design - S.A., M.E.; Data Collection or Processing - N.S.D.; Analysis or Interpretation - M.E.; Literature Search - N.S.D.; Writing- S.A., M.E.

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

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## References

1. Akkermans MD, Mieke Houdijk ECA, Bakker B, Boers AC, van der Kaay DCM, de Vries MC, et al. Iron status and its association with HbA1c levels in Dutch children with diabetes mellitus type 1. Eur J Pediatr 2018; 177: 603-10.
2. Wojciak RW, Mojs E, Stanislawska-Kubiak M. The occurrence of iron-deficiency anemia in children with type 1 diabetes. J Investig Med 2014; 62: 865-7.
3. Gallager EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes. J Diabetes 2009;1: 9-17.
4. Tarim O, Küçükerdoğan A, Gunay U, Eralp O, Ercan I. Effects of iron deficiency anemia on hemoglobin A1c in type 1 diabetes mellitus. Pediatr Int 1999; 41: 357-62.
5. Salah N, El Hamid FA, Abdelghaffar S, El Sayem M. Prevalence and type of anaemia in young Egyptian patients with type 1 diabetes mellitus. East Mediterr Health J 2005; 11: 959-67.
6. Ito H, Takeuchi Y, Ishida H, Otawa A, Shibayama A, Antoku S, et al. Mild anemia is frequent and associated with micro- and macroangiopathies in patients with type 2 diabetes mellitus. J Diabetes Investig 2010; 1: 273-8.
7. Ezenwaka CE, Jones-LeCointe A, Nwagbara E, Seales D, Okali F. Anaemia and kidney dysfunction in Caribbean type 2 diabetic patients. Cardiovasc Diabetol 2008; 7: 25.
8. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; (37 Suppl 1): S81-90.
9. Rusak E, Rotarska-Mizera A, Adamczyk P, Mazur B, Polanska J, Chobot A. Markers of Anemia in Children with Type 1 Diabetes Journal of Diabetes Research. J Diabetes Res 2018; 2018: 5184354.
10. Forte G, Bocca B, Peruzzu A, Tolu F, Asara Y, Farace C, et al. Blood metals concentration in type 1 and type 2 diabetics. Biol Trace Elem Res 2013; 156: 79-90.
11. Raj S, Rajan GV. Correlation between elevated serum ferritin and HbA1c in type 2 diabetes mellitus. Int J Res Med Sci 2013; 1: 12-5.
12. Ahmad J, Rafat D. HbA1c and iron deficiency: a review. Diabetes Metab Syndr 2013; 7: 118-22.
13. English E, Idris I, Smith G, Dhatariya K, Kilpatrick ES, John WG. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review. Diabetologia 2015; 58: 1409-21.
14. Sinha N, Mishra TK, Singh T, Gupta N. Effect of iron deficiency anemia on hemoglobin A1clevels. Ann Lab Med 2012; 32: 17-22.

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# Duplex Kidney with a Segmental Solitary Cystic Dysplasia and Ureteric Atresia: A Rare Case

## Dupleks Böbrekte Segmenter Soliter Kistik Displazi ve Üreter Atrezisi: Nadir Bir Olgu

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## ABSTRACT

Dysplastic kidney cysts are developmental cysts of the kidney. They are mostly multi-cystic, and usually involve the whole kidney. In addition, the segmental and solitary form is rare. A one-year-old boy with an antenatal ultrasound diagnosis of a left kidney cyst was followed-up. Postnatal ultrasound examination revealed a duplex left kidney with a cystic dilatation in the upper pole and a normal appearing parenchyma in the lower pole. The cystic lesion (10×10 cm) with an upper polar location that did not show any regression was excised laparoscopically. The ureter communicating with the cystic component of the kidney was not seen on the left side during laparoscopy. Histopathologic diagnosis was a cystic renal dysplasia. We present a very rare case of a duplex kidney with a solitary dysplastic cyst and ureteric atresia and discuss the diagnostic and therapeutic process.

**Keywords:** Duplex kidney, cystic dysplasia, ureteral atresia, children

## ÖZ

Displastik böbrek kistleri böbreğin gelişimsel kistlerinden olup çoğunlukla multi-kistik ve genellikle tüm böbreği tutan patolojilerdir. Segmenter ve soliter formu nadirdir. Bir yaşında erkek olgu antenatal tanımlanmış sol böbrek kisti nedeni ile doğum sonrası takip edilmiş. İncelemelerinde solda dupleks böbrek, alt kutupta normal böbrek dokusu, üst kutbunda soliter kistik genişleme tespit edildi. Takiplerinde gerileme göstermeyen üst kutup yerleşimli kistik yapı (10x10 cm) laparoskopik olarak eksize edildi, üreteri görülmedi. Histopatolojisi kistik renal displazi olarak tanımlandı. Dupleks böbrek anomalisi ve aynı tarafta displazik kistik böbrek yapısı bulunan, üreteral atrezili olgu, çok nadir görülmesi ve tanı-tedavi süreçlerinin irdelenmesi için sunuldu.

**Anahtar Kelimeler:** Dupleks böbrek, kistik displazi, üreter atrezisi, çocuk

## Introduction

Multi-cystic dysplastic kidney (MCDK) is the most common form of renal dysplasia that is usually described as a cystic kidney enlargement during routine antenatal ultrasonographic examination. Dysplasia rarely occurs in solitarily form. The importance of the differentiation and definitive diagnosis of cystic kidney diseases lies in the fact that surgical treatment is not necessary unless complications, such as malignant transformation or hypertension, develop (1). In this study, we presented the clinical findings, imaging features, diagnosis, and treatment of a segmental solitary cystic dysplastic kidney (SSCDK). Our patient was being followed-up since a cystic kidney enlargement was detected by antenatal ultrasonography.

## Case Report

Verbal and written informed consent was obtained from the parents of the patient who participated in this study. Physical examination of the one-year-old boy with a left hypochondriac mass showed a left kidney upper pole cyst on ultrasonography. He had a history of left kidney hydronephrosis on antenatal ultrasonography.

Kidney ultrasonography revealed a smooth-edged upper pole cyst of the left kidney with dimensions of 10×10 cm. Intravenous urography showed a lucent mass displacing the calyces at the left upper pole. Mild calyceal dilatation was seen with a normal draining ureter in the lower pole (Figure 1). Lower pole of the kidney had a normal appearance (Figure 2), and a bifid pelvis was reported. Magnetic resonance urography showed

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a duplex collecting system with a double ureter. There was a normal ureter draining the lower pole of the kidney. There was also a dysgenetic dilated ureter with a blind proximal ending, having a separate bladder opening. The bladder was normal in the voiding cystourethrography, and reflux to the ureter was not seen (Figure 3).

The removal of the lesion by laparoscopic surgery was decided due to the growth of the mass and the compression symptoms. Orifices of the left and right ureters were seen during cystoscopy, which was performed under anaesthesia. There was no left complete double ureteric orifice, which was defined by the magnetic resonance imaging (MRI). The upper pole, which was in solitary cystic structure morphology, was excavated almost totally with the unroofing technique. No separate ureter was communicating with the upper pole. Histopathological diagnosis was a renal dysplasia. The final diagnosis was a left kidney segmental solitary dysplasia of the upper pole with a normal lower pole and duplex collecting system. After the 4th day of the surgery, the left kidney (lower pole), right kidney and bilateral ureters were evaluated and found as normal in the intravenous urography.

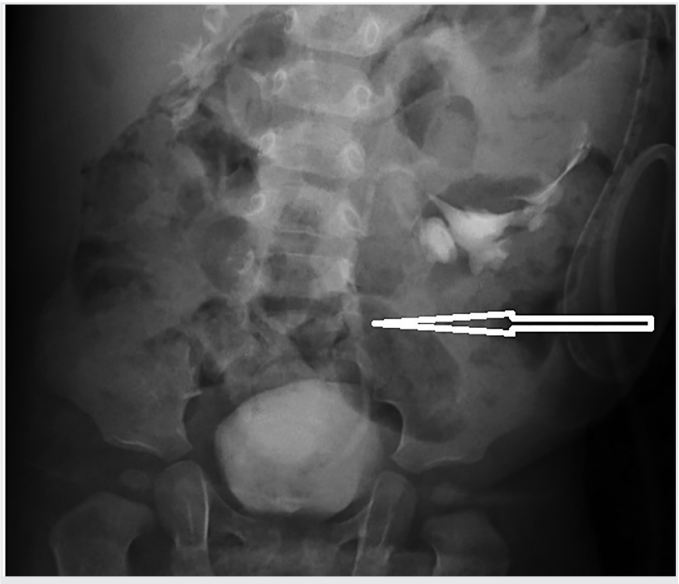

**Figure 1.** Intravenous urography shows a lucent defect displacing the calyces at the left upper pole. Mild calyceal dilatation is seen with a normal ureter draining the lower pole calyces

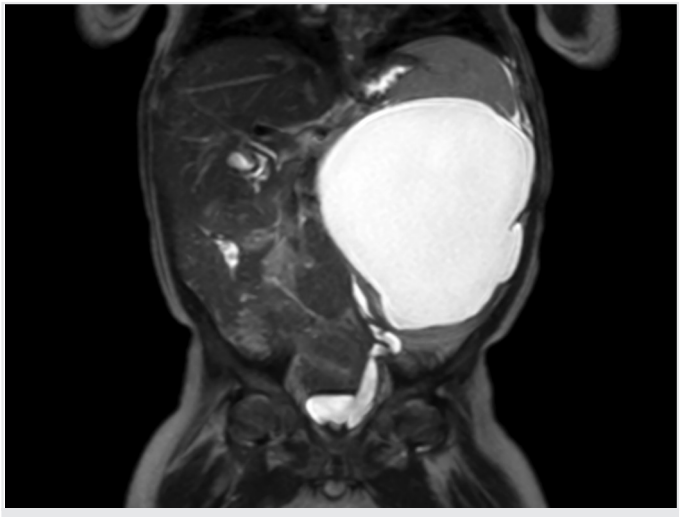

**Figure 2.** Coronal thick slab T2-weighted magnetic resonance urography shows a left-sided cystic kidney mass in the upper pole. A low lying dilated and tortuous left upper moiety ureter is seen

## Discussion

Dysplastic renal development anomalies are most commonly seen in the multi-cystic form. MCDK is the most common cause of abdominal mass in neonates following hydronephrosis. Renal dysplasia, the most common cystic disease in childhood, occurs during the metanephric phase of embryological development. If an obstruction occurs in the period after the embryological development, hydronephrosis instead of dysplasia will occur. The most common one is unilateral renal dysplasia. This form consists of 80%-90% of this anomaly, and occurs as a result of a pelvi-ureteral blockage of the entire kidney. If obstruction occurs at the infundibular level, the upper pole of the kidney can also be seen in a segmental or focal shape (1,2). Based on this information, it can be said that an infundibular blockage occurred at the late embryonic stage; therefore SSCDK was formed in our presented case.

SSCDK is rarer than MCDK, which has an occurrence rate of 1:4300 (3). These cases were first described as duplex kidneys and are difficult to identify because they have atypical clinical presentations. Abdominal mass occurs clinically in childhood, but it is sometimes not noticeable until adulthood. Patients sometimes apply to hospitals with complaints of recurrent urinary tract infections, abdominal pain, haematuria, and developmental delay (4). Since the SSCDK is a developmental anomaly, it may be accompanied by additional anomalies such as ureteropelvic obstruction, ureteral agenesis, dilatation of the collecting system without renal hypoplasia or ureterocoele, vesicoureteral reflux, malrotation, renal agenesis and horseshoe kidney. Less frequently, there are other abnormalities such as ectopic ureters opening in the dysplastic kidney or vesicoureteral reflux (5). The case did not have any findings other than the growing abdominal mass, and it was accompanied by a urethral atresia.

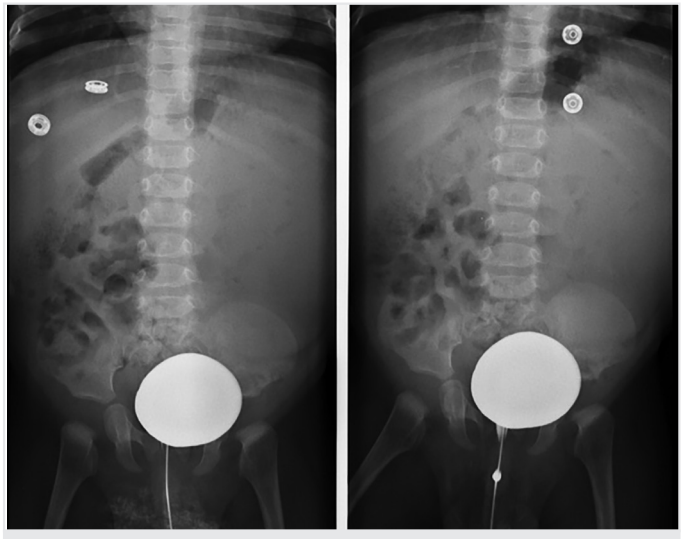

**Figure 3.** No vesicoureteral reflux is seen on voiding cystourethrogram

SSCDK can give the impression of a mass on abdominal radiography, with a kidney that is increased in size. Cyst wall calcifications are rarely seen in childhood, although they are seen in one third of cases among adults. Cystic structures replacing the normal kidney parenchyma is the ultrasonographic finding (6,7). In computed tomography and MRI, MCDK is a kidney mass composed of a large number of small cystic masses separated by non-associative septal defects with no contrast involvement (8-10). Due to the fact that the presented case is in the solitary form, there are not enough distinctive imaging findings in these cases and therefore, it was identified as hydronephrosis in the duplex kidney. The identification of the complete double-collector system was not confirmed by both cystoscopy and laparoscopy.

Histopathologic examination is used to distinguish various aetiologies among small kidneys, because this distinction is important for disease prognosis and genetic counselling. The diagnosis of renal dysplasia is not difficult; however, the diagnosis is sometimes confused with other conditions including polycystic kidney disease, foetal kidney, renal hypoplasia and renal atrophy. Histopathologically, some structures unique to the foetal stage such as metaplastic cartilage residues, hypoplasia, primitive mesenchymal tissues and canals are seen. Their number and size depends on whether they are hypoplastic or dysplastic. The absence of metaplastic cartilage tissue does not rule out renal dysplasia (4). In the presented case, the presence of primitive tubules and of cystic structures containing thin mesenchymal tissue confirmed the diagnosis of SSCDK.

As a result, SSCDK may occur with different clinical and radiological findings. For this reason, SSCDK should be included in the differential diagnosis of cystic kidney and cystic kidney masses. SSCDK are difficult to diagnose because they do not have pathognomonic imaging features, if there is no collector system duplication. In typical cases, SSCDK occurs at the upper pole. In symptomatic patients with the absence of involution, surgical treatment may be used instead of non-operative treatment, if there is hypertension.

**Ethics**

**Informed Consent:** Verbal and written informed consent was obtained from the parents of the patient who participated in this study.

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

**Authorship Contributions:** Surgical and Medical Practices- Ü.B., M.S., T.T. ; Concept- Ü.B., T.T., A.K. ; Design- Ü.B., T.T., A.K.P. ; Data Collection or Processing- M.S., A.K.P. ; Analysis or Interpretation- T.T., A.K.P. ; Literature Search- M.S., A.K. ; Writing- Ü.B., T.T., A.K.

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

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## References

1. Osathanondh V, Potter E. Pathogenesis of polycystic kidneys: type 2 due to inhibition of ampullary activity. Arch Pathol 1964; 77: 474-84.
2. Felson B, Cussen L. The hydronephrotic type of unilateral congenital multicystic disease of the kidney. Semin Roentgenol 1975; 2: 113-23.
3. Corrales JG, Elder JS. Segmental multicystic kidney and ipsilateral duplication anomalies. J Urol 1996; 155: 1398-401.
4. Chen RY, Chang H. Renal dysplasia. Arch Pathol Lab Med 2015; 139: 547-51.
5. Cascio S, Paran S, Puri P. Associated urological anomalies in children with unilateral renal agenesis. J Urol 1999; 162(3 Pt 2): 1081-3.
6. Sarmiento de la Iglesia MM, Peña B, Lecumberri G, Oleaga L, Grande Icaran D. Segmental multicystic renal dysplasia: radiological findings and differential diagnosis. Radiologia 2007; 49: 269-71.
7. Heymans C, Breysem L, Proesmans W. Multicystic kidney dysplasia: a prospective study or natural history of the affected and contralateral kidney. Eur J Pediatr 1998; 157: 673-5.
8. Jeon A, Cramer B, Walsh E, Pushpanathan C. A spectrum of segmental multicystic renal dysplasia. Pediatr Radiol 1999; 29: 309-15.
9. Cardona-Grau D, Kogan BA. Update on Multicystic Dysplastic Kidney. Curr Urol Rep 2015; 16: 67.
10. Carmack AJK, Castellan M, Perez-Brayfield M, Gosalbez R. Segmental multicystic dysplasia and ureteropelvic junction obstruction in a nonduplicated kidney. J Pediatr Surg 2006; 41: e1-3.

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# The Importance of Simultaneous Surgical and Endoscopic Polypectomies in Peutz-Jeghers Syndrome: A Case Report

## Peutz-Jeghers Sendromunda Eş Zamanlı Cerrahi ve Endoskopik Polipektominin Önemi: Olgu Sunumu

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## ABSTRACT

Peutz-Jeghers syndrome may be presented with gastrointestinal and extra-intestinal malignancies. Herein, we report a case of Peutz-Jeghers syndrome with a malignant intestinal polyp accompanied by synchronous multiple hamartomatous gastrointestinal polyps that was treated with simultaneous surgical and endoscopic polypectomies.

**Keywords:** Peutz-Jeghers syndrome, polyps, adenocarcinoma, endoscopy, general surgery

## ÖZ

Peutz-Jeghers sendromu, gastrointestinal ve ekstraintestinal maligniteler ile prezente olabilir. Yaygın hamartomatöz gastrointestinal polipler ile senkron bir malign ince bağırsak polibi olan, eş zamanlı cerrahi ve endoskopik polipektomiler ile operatif tedavi uygulanan Peutz-Jeghers sendromu olgusunu sunmayı amaçladık.

**Anahtar Kelimeler:** Peutz-Jeghers sendromu, polipler, adenokarsinom, endoskopi, genel cerrahi

## Introduction

Peutz-Jeghers syndrome (PJS) is an autosomal dominant, hereditary syndrome, characterised by hamartomatous gastrointestinal polyps. Patients may present with hyperpigmented spots in the lips and oral mucosa, abdominal pain, haematochezia and anaemia (1). Herein, we report a case who was diagnosed with PJS, had a past history of multiple colonoscopic polypectomies and surgical enterotomic polypectomy procedures between 1996 and 2006 and was eventually re-operated on due to the ongoing formation of multiple polyps in the colon, small intestine and stomach.

## Case Report

A 32-years-old man with a past history of multiple surgical and colonoscopic polypectomies, was admitted to our clinic, after he was recently diagnosed with multiple gastrointestinal polyps in various localisations during his long term follow-ups. His father and five siblings were also diagnosed with PJS. Upper gastrointestinal endoscopy of the patient revealed multiple small polypoid lesions in the stomach and duodenum. In addition to the multiple diminutive and pedunculated polyps, a large-pedunculated, lobulated, giant polyp with a size of 5×5 cm in the sigmoid colon was found during colonoscopy. There were also 3 diminutive polyps in the proximal transverse colon. Abdominal magnetic resonance imaging (MRI) revealed focal dilations accompanied by diffuse hypo-intense areas filling the small intestinal lumen and suspected contrast enhancements within these mass lesions. Additionally, MRI revealed a contrast enhanced irregular mass lesion, filling approximately 50% of the sigmoid colon lumen that extended along a segment of 6.5 cm. After obtaining a written informed consent from the patient, he was admitted to the general surgery department and underwent surgery. The surgical abdominal exploration revealed multiple, intraluminal palpable small intestinal polypoid lesions starting from the proximal jejunum and continuing approximately 150 cm distally from the ligament of Treitz. On the other hand, since the colonic polyps were found to be soft in texture on palpation, it was decided to perform an intraoperative colonoscopy to determine the exact location of the large sigmoid polyp, which showed hundreds of millimetric polyps throughout the colon, in addition to the giant pedunculated 6-cm-sized polyp in the sigmoid colon (Figure 1). Intraoperative enteroscopy performed via an

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enterotomy 70 cm distal to the ligament of Treitz showed hundreds of subcentimetric polyps. Multiple surgical and endoscopic polypectomies were performed via enterotomies created at 70, 100 and 120 cm distally from the ligament of Treitz (Figure 2). Segmental colon resection with clear surgical margins and end-to-end anastomosis were performed due to the giant polyp in the sigmoid colon. The patient was discharged on the 8th postoperative day without any postoperative complications. Histopathological examination revealed a total number of 52 polyps. There was a pedunculated hamartamatous intestinal polyp with diameters of 3.5×2 ×1.7 cm, located in a jejunal segment 90 cm distally to the ligament of Treitz, the histopathology of which was found to be a well differentiated intramucosal adenocarcinoma. The carcinoma had a size of 0.2 cm and its distance to the surgical margin was approximately 1 cm. The stage of this lesion was defined as pTis N0 M0 according to the American Joint Committee on Cancer tumor-node-metastasis staging system (Figure 3). Additionally, four of the polyps located at the jejunal segments 0, 10, 60 and 70 cm distally to the ligament of Treitz were found histopathologically to be focally low-graded hamartomatous polyps with adenomatous changes. All of the other polypectomy specimens were defined as hamartomatous polyps. Histopathological review of the segmental sigmoid colon resection material revealed a 6-cm-sized lobulated giant polypoid lesion formed by a collection of multiple hamartomatous polyps.

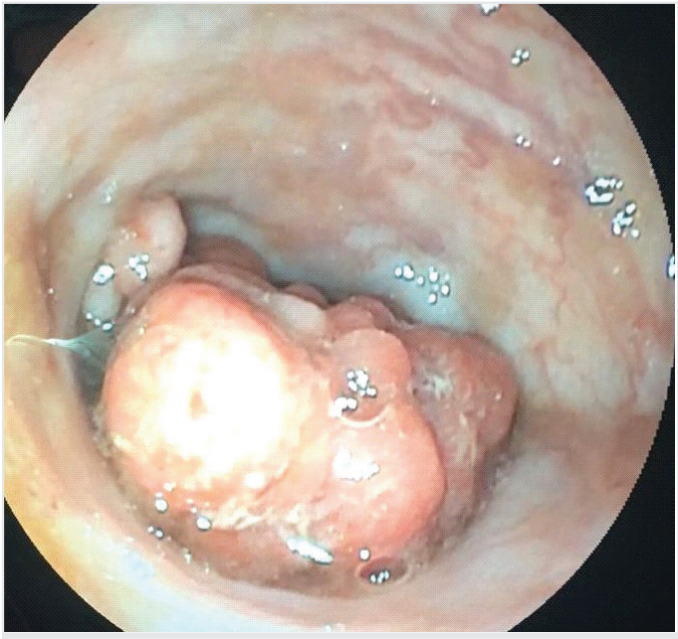

**Figure 1.** Colonoscopic image of the pedunculated 6-cm-sized giant polyp in the sigmoid colon

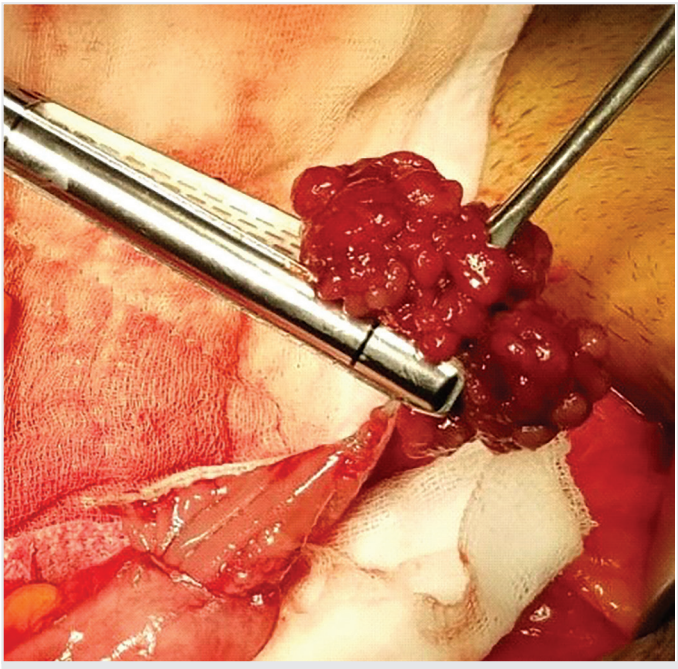

**Figure 2.** Mucosal polyp excision via enterotomy

## Discussion

PJS is an autosomal dominant inherited disorder with an estimated incidence of 1:50,000-1:200,000, characterised by mucocutaneous melanin pigmentation and gastrointestinal hamartomatous polyps (1). *STK11/LKB1* gene mutation has been proven as an etiological factor of PJS and 70% of PJS patients have a positive family history (1,2). Most PJS polyps are of the hamartomatous type, and they are mostly reported to be localised in the jejunum, colon, rectum, duodenum and stomach, respectively; nonetheless, they can be present in the entire gastrointestinal tract (3). We report a case that presented with multiple gastric, duodenal, jejunal and colonic hamartomatous polyps.

PJS is a disorder with an increased susceptibility for tumours, and it is also a predisposing factor for gastrointestinal and non-gastrointestinal malignancies (4). Tumour incidence in PJS patients is 15 times greater than in the general population, whereas malignancy incidence is approximately 20% (3). The lifetime risk of developing gastrointestinal malignancies among PJS patients is estimated as 39% for colon cancer, 36% for pancreatic cancer, 29% for gastric cancer, 19% for intestinal cancer and 0.5% for oesophageal cancer (4). Additionally, for non-gastrointestinal malignancies, estimated risks are determined as 54% for breast cancer, 21% for ovarian cancer, 15% for lung cancer and 9% for endometrial cancer (5). Studies have shown that the cancer

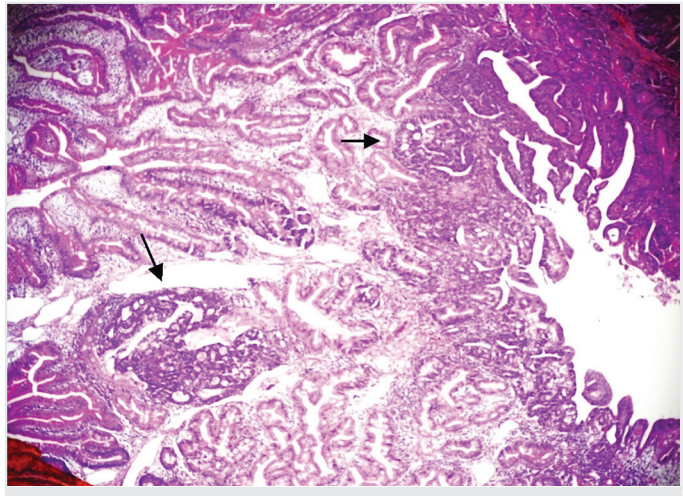

**Figure 3.** Intramucosal adenocarcinoma developed in a hamartomatous polyp (H&E ×40)

predisposition is not only due to the mutation in the *STK11* gene, but is also associated with the hamartoma-adenoma-carcinoma sequence or directly with the hamartoma-carcinoma transition (6). In the presented case, a total number of 52 intestinal and colonic polyps were removed, and one of the intestinal polyps was detected to harbour a focus of intramucosal adenocarcinoma.

PJS patients clinically present with symptoms such as intestinal obstruction (43%), abdominal pain (23%), gastrointestinal system haemorrhage (14%), hyperpigmented skin (13%) and the presence of anal polyps (7%) (5). Acute mechanical intestinal obstruction, which can be caused by various conditions such as invagination and malignancy, is one of the most common complications of PJS (6). Invagination is a severe complication that can occur in 47% of younger patients (1,5). Family members of PJS patients also have a high incidence of the syndrome and therefore, screening protocols have been developed for the first degree relatives of PJS patients who are considered to be in the high risk group (1). These individuals must have annual examinations beginning at birth for the hyperpigmented lesions. Due to the high risk of invagination-related obstruction seen in the early ages, asymptomatic children at risk may be advised to take a test at the age of 8 for the mutation in the *STK11* gene. The case presented herein had a family history of PJS, as well as a history of previous surgical and endoscopic polypectomies. Therefore, he was being followed-up endoscopically and an elective surgery was performed due to the recent findings of multiple polypoid lesions detected during his long term follow-ups.

Imaging methods such as magnetic resonance enterography and barium series may be recommended for adults. Upper gastrointestinal tract and intestinal endoscopy as well as colonoscopy are also recommended by various authors at the ages of 12, 18 and 24 years, respectively (7).

One of the leading PJS-related cancers is breast cancer (32%-54%). The incidence rate of PJS-related breast cancer is similar to that of the *BRCA 1-2* gene-related breast and ovarian cancers (4). Hence, the same breast cancer screening recommendations are used for patients with PJS and *BRCA 1-2* mutations (1). Breast examination on a monthly basis starting from the age of 18, annual MRIs and/or ultrasonographies since the age of 25 and regular mammographic screenings are recommended (7).

Colorectal cancers are the second most common cancers associated with PJS. Colonoscopic examinations starting from the age of 18 or 5-10 years before the earliest occurrence of cancer in the family members, and repeating the colonoscopy within 2-3 years are recommended (1). Since a giant sigmoid polyp was detected in the presented case, a segmental sigmoid resection was performed because of the risk of colon cancer that could be associated with PJS. However, the histopathological examination of this lesion revealed that it was a collection of multiple hamartomatous polyps that did not harbour any malignant foci.

Pancreatic cancer is the third most common malignancy and often starts at the ages of 25-30; annual screening methods such as endoscopic ultrasonography, MRI and magnetic resonance cholangiopancreatography may be planned (1).

The incidence of gastric cancer is approximately 29%, whereas that of intestinal cancer is 13%. Therefore, upper gastrointestinal endoscopic surveillance with an interval of 2-3 years, starting from the age of 18 is recommended. Capsule endoscopy may be used as well (8,9). For gastric and colonic polyps larger than 1 cm, polypectomy via endoscopy is recommended (9). Surgical excision is recommended for asymptomatic polyps larger than 1.5 cm or symptomatic/fast growing polyps (9). Upper gastrointestinal endoscopy of our patient revealed multiple small polypoid lesions in the stomach and duodenum, and it was decided to be reserved for continued endoscopic surveillance, whereas it was decided that the polyps detected throughout the small intestinal and colonic lumen be removed surgically.

All the palpable intraluminal lesions must be resected in case of emergency and/or elective laparotomies, on account of the fact that intestinal lesions may be overlooked during endoscopic surveillance, and because there is a risk of malignancy related to PJS (6). In order to clear the entire intestinal system of polyps, intraoperative endoscopies, and in cases of larger polyps, enterotomies are recommended (2,6,10). This "clean sweep" approach is identified as a solution that minimises the requirement for recurrent small bowel surgeries (10). In this context, we performed multiple intestinal and colonic surgical polypectomies in our case with the use of intraoperative enteroscopy and colonoscopy, in addition to a segmental colon resection with the aim of cleaning all the polyps that could be localised during surgery.

Since hamartomas in patients with PJS possess a risk of malignancy, these cases must be strictly followed-up, thus for newly developed polyps, endoscopic polypectomies must be performed, and in case of necessity for a surgical intervention, all facilities including intraoperative endoscopy must be used in order to remove the polyps completely.

**Ethics**

**Informed Consent:** Written informed consent was obtained from the patient for being included in the case report.

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

**Authorship Contributions:** Surgical and Medical Practices- T.E., H.Ş., A.G., İ.A.Ö., Ö.E., O.A. ; Concept- D.B., T.E., A.G., Ö.E., O.A. ; Design- D.B., T.E., A.G., Ö.E., O.A. ; Data Collection or Processing- D.B., T.E., A.G., H.Ş., İ.A.Ö. ; Analysis or Interpretation- T.E., A.G., H.Ş., İ.A.Ö., Ö.E., O.A. ; Literature Search- D.B., T.E., A.G., İ.A.Ö. ; Writing- D.B., T.E., A.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.

## References

1. Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol 2006; 4: 408-15.
2. Alimoğlu O, Sahin M, Cefle K, Celik O, Eryilmaz R, Palandüz S. Peutz-Jeghers syndrome: Report of 6 cases in a family and management of polyps with intraoperative endoscopy. Turk J Gastroenterol 2004; 15: 164-8.
3. Sharma M, Singh R, Grover AS. Peutz-jeghers syndrome with synchronous adenocarcinoma arising from ileal polyps. Indian J Surg 2015; 77(Suppl 1): 100-2.
4. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV. Very high risk of cancer on familial Peutz-Jeghers syndrome. Gastroenterology 2000; 119: 1447-53.

5. Wangler MF, Chavan R, Hicks MJ, Nuchtern JG, Hegde M, Plon SE, et al. Unusually early presentation of small-bowel adenocarcinoma in a patient with Peutz-Jeghers syndrome. J Pediatr Hematol Oncol 2013; 35: 323-8.

6. Eren T, Bayraktar B, Celik Y, Boluk S, Adali G. Acute malignant intestinal obstruction accompanied by synchronous multifocal intestinal cancer in Peutz-Jeghers syndrome: report of a case. Surg Today 2012; 42: 1125-9.

7. Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 2010; 59: 975-86.

8. Hinds R, Philp C, Hyer W, Fell JM. Complications of childhood Peutz-Jeghers syndrome: implications for pediatric screening. J Pediatr Gastroenterol Nutr 2004; 39: 219-20.

9. Giardiello FM. Gastrointestinal polyposis syndromes and hereditary nonpolyposis colorectal cancer. In: Rustgi AK (ed). Gastrointestinal cancers: biology, diagnosis, and therapy. Philadelphia: Lippincott-Raven Publishers; 1995.p.370-1.

10. Oncel M, Remzi FH, Church JM, Connor JT, Fazio VW. Benefits of 'clean sweep' in Peutz-Jeghers patients. Colorectal Dis 2004; 6: 332-5.