

# ENT updates



An International Journal of ENT and Related Subjects

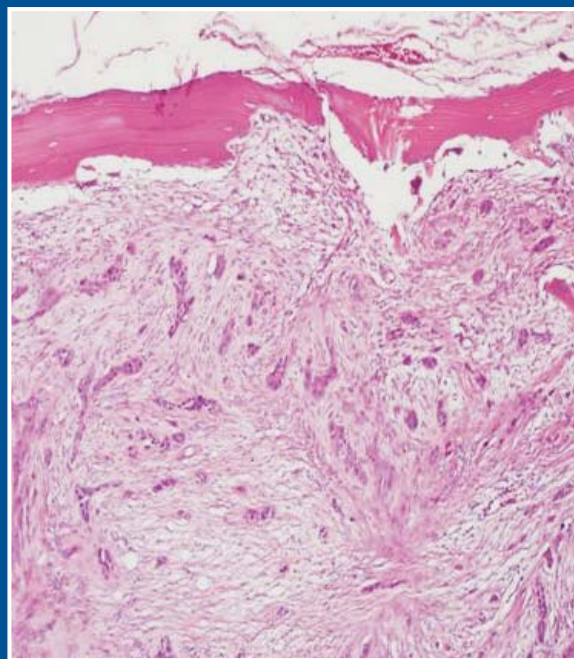
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### Aims and Scope

The goal of the journal is to present and improve collective scientific knowledge and the scientific background dealing with otorhinolaryngological disorders and related subjects (allergy, pediatrics, neurology, psychiatry, neurosurgery, radiology, anesthesiology, pulmonology, etc.) via experimental and clinical studies, reviews, case reports, short communications and letters to the editor. The initial aim of this journal is to form a countrywide education platform and to share the recent information and learn about the treatment of various local or rare diseases in aware of the fact that a disease may be rare to a certain region while it is very common to another. The second aim of this journal and Continuous Education and Scientific Research Association (CESRA), a nonprofit organization serving for continuous education, is to represent our country in international arena of science and knowledge with the published papers. We aimed to undertake a novel effort in the international representation and attribution of published articles. That is why we have set an international editorial board from all over the world beside the national board spread to each corner of the country. The target readers of the ENT Updates include otorhinolaryngology specialists and residents as well as all other physicians working in the field of otorhinolaryngology or in related specialities.

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## Improvement in science, and publication



Cemal Cingi

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Dear Colleagues,

As we stepped up to sixth year of our publication, it is my great pleasure and excitement to announce you that our journal “**ENT Updates**” has been included by Thomson Reuters to ESCI (Emerging Sources Citation Index).

I believe that it will bring our journal significant scientific improvement and international recognition. We are looking forward for your papers.

As always, I would like to invite you to submit your latest manuscripts to “**ENT Updates**”. I promise a fast but meticulous review and final decision.

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Please do not hesitate to contact me if you have any questions about the journal or to volunteer to be a reviewer.

Best regards,  
Cemal Cingi, MD  
Editor-in-Chief

# Cytokine gene polymorphisms and expression in Turkish pediatric cochlear implant patients

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## Abstract

**Objective:** We assessed the association between the polymorphisms and expressions of three cytokine genes and clinical parameters in children who underwent cochlear implantation due to profound congenital sensorineural hearing loss.

**Methods:** We analyzed the IL-6/-174, IFN- $\gamma$ /+874 and TNF- $\alpha$ /-308 genes in 64 cases with congenital sensorineural hearing loss and in 70 healthy controls. Cytokine genotyping/expression was performed using the PCR-SSP method.

**Results:** No significant differences were detected between the patient group and the healthy controls with respect to the distributions and numbers of genotypes and alleles of TNF- $\alpha$  or IL-6. However, the TT genotype, associated with high expression of IFN- $\gamma$ , and the T allele frequency were significantly more frequent in the patient group versus the controls ( $p=0.016$  and  $0.023$ , respectively).

**Conclusion:** Our results suggest that high expression of the IFN- $\gamma$  gene may be associated with susceptibility to the disease. Consequently, IFN- $\gamma$  may be a useful marker of the etiopathogenesis of congenital sensorineural hearing loss.

**Keywords:** Congenital sensorineural hearing loss, cytokine gene, variation.

## Özet: Sitokin geni polimorfizmleri ve Türk pediyatrik koklear implant hastalarındaki ekspresyonu

**Amaç:** Çalışmamızda polimorfizmler, üç adet sitokin geni ekspresyonu ve konjenital sensorinöral işitme kaybı tedavisi için koklear implantasyon uygulanmış çocukların klinik parametreleri arasındaki ilişkiyi inceledik.

**Yöntem:** IL-6/-174, IFN- $\gamma$ /+874 ve TNF- $\alpha$ /-308 genleri, 64 konjenital sensorinöral işitme kaybı hastasında ve 70 sağlıklı kontrol olgusunda analiz edildi. Sitokin ekspresyonu PCR-SSP yöntemi ile gerçekleştirilmiştir.

**Bulgular:** Hasta grubu ve sağlıklı kontrol grubu arasında TNF- $\alpha$  veya IL-6'nın genotipleri ve allel frekansları sayısı ve dağılımı bakımından belirgin bir farklılık saptanmadı. Ancak yüksek IFN- $\gamma$  ekspresyonu ile ilişkilendirilen TT genotipi ve T allel frekansı, hasta grubunda kontrol grubuna göre daha sıklıkla gözlemlendi (sırasıyla  $p=0.016$  ve  $p=0.023$ ).

**Sonuç:** Sonuçlarımız yüksek oranda IFN- $\gamma$  geni ekspresyonunun hastalığa olan duyarlılığı artırdığını göstermiştir. Bunu takiben IFN- $\gamma$  geninin konjenital işitme kaybının etiopatogenezinde yararlı bir belirteç olabileceği sonucu ortaya çıkmıştır.

**Anahtar sözcükler:** Konjenital işitme kaybı, sitokin geni, varyasyon.

Congenital hearing loss is a common birth defect that affects approximately 1–3 children per 1000 births.<sup>[1]</sup> Among the etiological factors affecting prelingual deaf patients, 60% are hereditary, while 40% are environmental or iatrogenic.<sup>[1,2]</sup> The etiology of congenital sensorineural hearing loss remains largely unknown. One hypothesis is that immuno-

logical factors are responsible for disease development.<sup>[3,4]</sup> Moreover, single nucleotide polymorphisms (SNPs) at position -308 of the TNF- $\alpha$  gene, at position -174 of the IL-6 gene, and at position +874 of the interferon-gamma (IFN- $\gamma$ ) gene were previously shown to be associated with inflammatory and autoimmune disorders.<sup>[5,6]</sup>

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TNF- $\alpha$  is a potent immunomodulatory and proinflammatory cytokine that mediates inflammatory diseases and is produced by activated macrophages.<sup>[7,8]</sup> TNF- $\alpha$  (-308) AA and AG genotypes have the potential to produce higher levels of TNF- $\alpha$ , whereas the GG genotype produces lower levels of TNF- $\alpha$ .<sup>[9]</sup> IL-6 is a proinflammatory cytokine and plays a key role in acute and chronic inflammation, affecting the endocrine and other systems, such as the central nervous and cardiovascular systems.<sup>[10]</sup> Both the GG and GC genotypes of IL 6 (-174) are associated with increased levels of IL-6, while the CC genotype leads to decreased expression of this cytokine.<sup>[11]</sup> IFN- $\gamma$  has immunomodulatory, antimicrobial, antiproliferative, and antifibrotic activities and also modulates the production or activities of several cytokines.<sup>[12]</sup> The IFN- $\gamma$  (+874) AA genotype is associated with lower production, TA with intermediate production, and TT with higher production of this cytokine.<sup>[13]</sup> The aim of this study was to explore any association between the polymorphisms and expression levels of the three cytokine genes and clinical parameters in children who underwent cochlear implantation because of profound congenital sensorineural hearing loss.

## Materials and Methods

In total, 64 unrelated patients with suspicion of congenital sensorineural hearing loss and 70 healthy controls were included in this study. The patients had no history of perinatal infections, and tests for viral markers for hepatitis and

HIV were negative. Patients with syndromic hearing loss, malformed inner ears, or multiple handicaps were excluded. The preoperative evaluation included a medical history, a physical examination, and a battery of audiological tests (otoacoustic emissions, evoked response audiometry, behavioral audiometry, and ASSR). Imaging studies of the temporal bone were also performed. All the children then underwent cochlear implantation with Med-El (MED-EL, Innsbruck, Austria) or Nucleus (Cochlear Corp., Lane Cove, New South Wales, Australia) cochlear implants. The study was approved by the University of Gaziantep Ethics Committee of Clinical Research. All parents of the children gave their informed consent for inclusion in this study. DNA was isolated from blood samples and the IL-6/-174, IFN- $\gamma$ /+874, and TNF- $\alpha$ /-308 cytokine genes were analyzed. Cytokine genotyping/expression testing was performed using the PCR-SSP method,<sup>[14]</sup> and all data were analyzed using the de Finetti program<sup>[15]</sup> and SPSS software (ver. 14.0 for Windows; SPSS Inc., Chicago, IL, USA).

## Results

Allele frequencies and genotype distributions of the IL-6, IFN- $\gamma$ , and TNF- $\alpha$  genes in patients and controls are shown in Table 1. There were no significant differences between the patient group and healthy controls among the distribution or number of genotypes and alleles for TNF- $\alpha$  or IL-6. The TT genotype, associated with higher IFN-

**Table 1.** Genotype distribution/expression and allele frequencies of the TNF- $\alpha$ , IL-6 and IFN- $\gamma$  genes in patients with congenital sensorineural hearing loss and in controls.

	Genotype/ allele	Patients n* (%)	Healthy control n† (%)	OR (95% CI)	p value
TNF- $\alpha$ (-308)	GG <sup>§</sup>	52 (81.3)	58 (82.9)	0.89 (0.37–2.16)	0.4933
	AG <sup>‡</sup>	11 (17.2)	10 (14.3)	1.24 (0.48–3.16)	0.4115
	AA <sup>‡</sup>	1 (1.5)	2 (2.8)	0.53 (0.04–6.10)	0.5338 <sup>  </sup>
	G allele	115 (89.8)	126 (90)	1.01 (0.45–2.25)	0.4831
	A allele	13 (10.2)	14 (10)	0.98 (0.44–2.17)	0.4831
IFN- $\gamma$ (+874)	TT <sup>‡</sup>	15 (23.4)	6 (8.6)	3.26 (1.180–9.033)	0.0162 <sup>  </sup>
	TA <sup>¶</sup>	31 (48.5)	37 (52.9)	0.83 (0.42–1.65)	0.3676
	AA <sup>§</sup>	18 (28.1)	27 (38.5)	0.62 (0.30–1.29)	0.1366
	T allele	61 (47.7)	49 (35)	1.69 (1.03–2.76)	0.0239 <sup>  </sup>
	A allele	67 (52.3)	91 (65)	0.59 (0.36–0.96)	0.0239
IL-6 (-174)	GG <sup>‡</sup>	29 (45.3)	41 (58.6)	0.58 (0.29–1.16)	0.0866
	GC <sup>‡</sup>	30 (46.9)	25 (35.7)	1.58 (0.79–3.17)	0.1280
	CC <sup>§</sup>	5 (7.8)	4 (5.7)	1.39 (0.35–5.45)	0.4433 <sup>  </sup>
	G allele	88 (68.8)	107 (76.4)	0.67 (0.39–1.16)	0.1015
	C allele	40 (31.2)	33 (23.6)	1.47 (0.85–2.53)	0.1015

\*n=64, †n=70, ‡high expression, §low expression, ||Fisher's exact Test, ¶intermediate expression.

$\gamma$  expression, and the T allele frequency were found to be significantly more frequent in the patient group than in the controls ( $p=0.016$  and  $0.023$ , respectively). The observed genotype counts did not deviate significantly from those expected according to Hardy-Weinberg equilibrium ( $p>0.05$ ). No relationship was found between the cytokine genotypes and clinical parameters of the patients.

## Discussion

IFN- $\gamma$  or type II interferon is a cytokine vital for innate and adaptive immunity against viral infections and intracellular bacterial infections and for tumor control. Aberrant IFN- $\gamma$  expression is associated with numerous autoinflammatory and autoimmune diseases.<sup>[6]</sup> The significance of IFN- $\gamma$  in the immune system stems partly from its ability to directly inhibit viral replication. Most importantly, its immunostimulatory and immunomodulatory effects are mediated predominantly by natural killer (NK) and natural killer T (NKT) cells as part of the innate immune response (and by CD4 and CD8 cytotoxic T lymphocytes (CTLs), which are effector T cells, once antigen-specific immunity develops). A functional SNP at position +874 of the human IFN- $\gamma$  gene, correlating with differential cytokine production, was reported by Pravica et al.<sup>[6,14,16]</sup> The polymorphism lies within a binding site for the transcription factor NF- $\kappa$ B, and electrophoretic mobility shift assays showed specific binding of NF- $\kappa$ B to the allelic sequence containing the +874T allele. As this transcription factor induces IFN- $\gamma$  expression, the +874T and +874A alleles likely correlate with high and low IFN- $\gamma$  expression, respectively. The transcription factor NF- $\kappa$ B also preferentially binds to the +874T allele, which was overrepresented in the controls, suggesting that genetically determined variability in IFN- $\gamma$  expression may be important for the development of tuberculosis.<sup>[16-19]</sup> Neutralizing IFN- $\gamma$  completely prevented both vascular dysfunction and changes in NOS expression, and neutralizing TNF reduced IFN- $\gamma$  production and partially prevented dysfunction. Inhibiting iNOS partially preserved responses to NO at two weeks and reduced graft intimal expansion after four weeks in vivo. In fact, Koh et al. concluded that IFN- $\gamma$  was a central mediator of vascular dysfunction through the dysregulation of NO production. Adhesion development was also found to depend on the IFN- $\gamma$  and STAT1 system, and NKT cell-deficient mice developed poor adhesion. However, these mice developed severe adhesion after reconstitution with NKT cells from wild-type mice, suggesting that the production of IFN- $\gamma$  by NKT cells is indispensable for adhesion formation.<sup>[20]</sup> In a study by Alper et al., it is suggested that IFN- $\gamma$  gene polymorphism

predisposes a patient to otitis during an upper respiratory infection.<sup>[5]</sup> Matkovic et al. studied the cytokine levels of bilateral ears in patients with otitis media with effusion and they found that the immune response of the same patient can be different in each ear.<sup>[21]</sup> Aminpour et al. studied the role of TNF- $\alpha$  in patients with sensorineural hearing loss after bacterial meningitis and they concluded that TNF- $\alpha$  plays an important role in cochlear injury after bacterial meningitis.<sup>[22]</sup> According to these findings, if there is an intrauterine infection and inflammation even the immune response of the same patient might be different and this immune response can result with susceptibility for cochlear injury. According to the results of this study, silent infections in the perinatal period may contribute to congenital profound sensorineural hearing loss. To the best of our knowledge, the relationship between cytokine genotypes/expression and clinical parameters in patients with congenital hearing loss has not been investigated. Our results suggest that high expression of the IFN- $\gamma$  gene may be associated with susceptibility to the disease.

## Conclusion

Consequently, IFN- $\gamma$  may be a useful marker for disease etiopathogenesis in patients with congenital sensorineural hearing loss especially in patients who had perinatal silent infections. There are major limitations in this study; one is the limited number of the patients with hearing loss and the second one is the markers of major viral markers were not ruled out, this was because of the limited budget. Our results allow us to make only preliminary conclusions due to the small sample size. Further studies designed with eliminating major viral infectious diseases and with larger number of patients are needed.

**Conflict of Interest:** No conflicts declared.

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## Potential pitfalls of computed tomography in advanced laryngeal cancer

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### Abstract

**Objective:** In laryngeal cancer the most suspected regions of invasion are preepiglottic space (PES), anterior commissure (AC), thyroid cartilage (TC), subglottic region (SR) and extralaryngeal spread (ELS). The objective of this study is to compare the results of preoperative computed tomography (CT) with postoperative histopathologic analysis in these critical regions for the total or partial laryngectomy.

**Methods:** Eighty-nine patients, who had undergone total laryngectomy with a diagnosis of laryngeal cancer reported that squamous cell cancer (SCC) between 2005 and 2013, were reviewed retrospectively. All the patients, after the first application done total laryngectomy before flexible laryngoscopy, computed tomography for the neck and endoscopic biopsy with direct laryngoscopy. Histopathological results of PES, AC, TC, ELS and SR invasion are compared to preoperative CT findings and determined of specificity, sensitivity, false negative and false positive results and rate of accuracy.

**Results:** All the patients were male, median age was 67 (range: 48 to 81) years. Fifty-six patients were in T4 and 33 patients in T3 stage. Compared to results between positive CT findings and negative histopathological examination; PES invasion in 41 patients/ 5 patients, AC invasion was found in 38/ 15 patients, TC invasion in 28/16 patients, SR invasion in 49/ 9 patients and ELS invasion in 25 /7 patients. Accuracy rate of computed tomography in these regions are 85%, 64%, 76%, 79%, and 83%, respectively. All the results especially thyroid cartilage invasion were statistically significant.

**Conclusion:** In all regions invasion, CT has a low diagnostic reliability in high-grade laryngeal cancer in our study. We suggested that histopathological results are the gold standard intraoperatively for determining total or partial laryngectomy.

**Keywords:** Computed tomography, larynx carcinoma, accuracy.

### Özet: İleri evre larenks kanserinde bilgisayarlı tomografideki potansiyel tuzaklar

**Amaç:** Larenks kanserinde invazyonda en şüpheli alanlar preepiglottik boşluk (PEB), ön komissür (ÖK), tiroid kıkırdak (TK), subglottik bölge (SB) ve ekstralarengeal invazyon (ELY) varlığıdır. Çalışmadaki amacımız total ya da parsiyel larenjektomi için bu kritik bölgelerin preoperatif bilgisayarlı tomografi (BT) incelemesi ve postoperatif histopatolojik analizinin karşılaştırılmasıdır.

**Yöntem:** 2005–2013 yılları arasında raporda skuamöz hücreli kanser tanısı nedeniyle total larenjektomi uygulanan 89 larenks kanseri hastası retrospektif olarak incelendi. Hastaların hepsine başvuru sonrası fleksibl laringoskopi, boyuna yönelik bilgisayarlı tomografi ve sonrasında direkt larengoskopi eşliğinde endoskopik biyopsi yapılarak total larenjektomi uygulandı. Histopatolojik sonuçlar PEB, ÖK, TK, ELY ve SB invazyonları operasyon öncesi BT raporlarındaki invazyon sonuçlarıyla karşılaştırıldı, spesifite, sensitivite, yalancı negatif ve yalancı pozitif sonuçlar ile doğruluk oranları belirlendi.

**Bulgular:** Hastaların tümü erkekti ve yaş aralığı 48 ile 81 arasında olup ortalama yaş 67 bulundu. Elli altı hasta T4 evre, 33 hasta T3 evre larenks kanseri idi. BT’de pozitif, histopatolojik olarak negatif saptanan hastalar karşılaştırıldığında; PEB invazyonu 41/5 hasta, ÖK invazyonu 38/15 hasta, TK invazyonu 28/16 hasta, SB invazyonu 49/9 hasta ve ELY 25/7 hastada görüldü. BT’nin bu bölgelerdeki doğruluk oranları sırasıyla; %85, %64, %76, %79, %83 olarak bulundu. Özellikle tiroid kartilaj invazyonunda olmak üzere tüm sonuçlar istatistiksel olarak anlamlıydı.

**Sonuç:** Çalışmamızda ileri evre larenks kanserinde BT’nin tüm bahsedilen bölgelerde tanısız değerinin düşük olduğunu gördük. Total ya da parsiyel kararı vermede intraoperatif olarak histopatolojik değerlendirilmenin altın standart olduğu kanaatindeyiz.

**Anahtar sözcükler:** Bilgisayarlı tomografi, larenks kanseri, doğruluk.

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Laryngeal cancer is the second most common head and neck cancer after thyroid cancer. The 5-year survival rate exceeds 90% if the patient is diagnosed at an early stage and 60% to 70% otherwise.<sup>[1]</sup> The aim of surgery is to achieve local control while preserving the functions of speech and swallowing without a permanent tracheostomy. Conservative surgery with radiotherapy (RT) is a good option if possible.<sup>[2]</sup> However, total laryngectomy is required if there is extralaryngeal spread (ELS) or invasion of the pre-epiglottic space (PES), thyroid cartilage (TC), arytenoid cartilage (AC), SR, or interarytenoid region.<sup>[3]</sup>

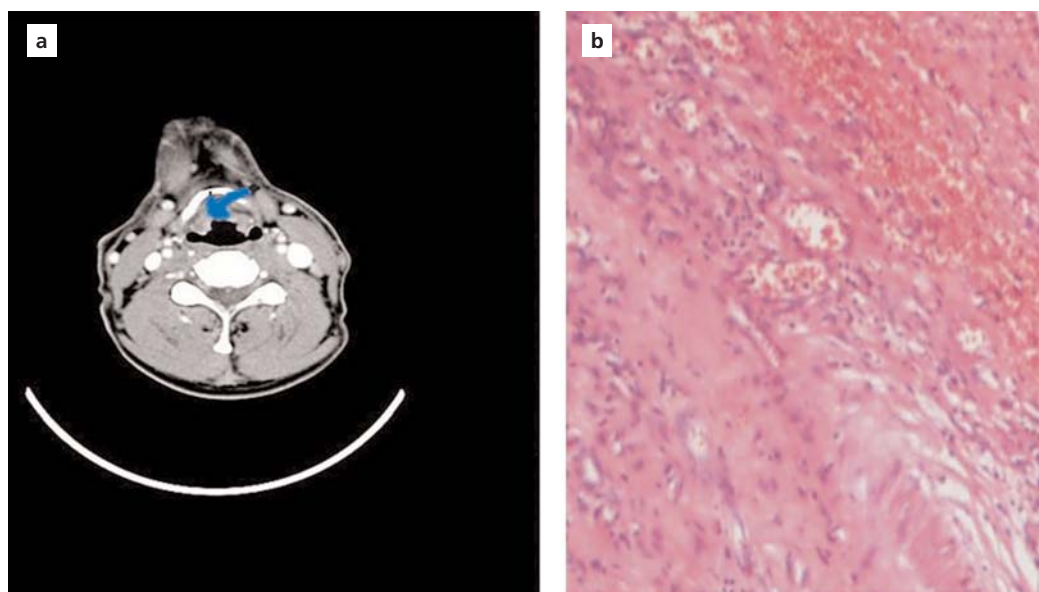
Before planning cancer surgery, staging is important and might necessitate indirect laryngoscopy, imaging, and biopsy under direct laryngoscopy.<sup>[4]</sup> However, submucosal and deep invasion cannot be identified with indirect or direct laryngoscopy. Sagittal or coronal radiological imaging should be performed to detect ELS and deep invasion, especially of the PES, AC, SR, and TC.<sup>[5]</sup> This report compares computed tomography (CT) findings with surgical and histopathological findings to determine the reliability of CT in advanced laryngeal cancer.

## Materials and Methods

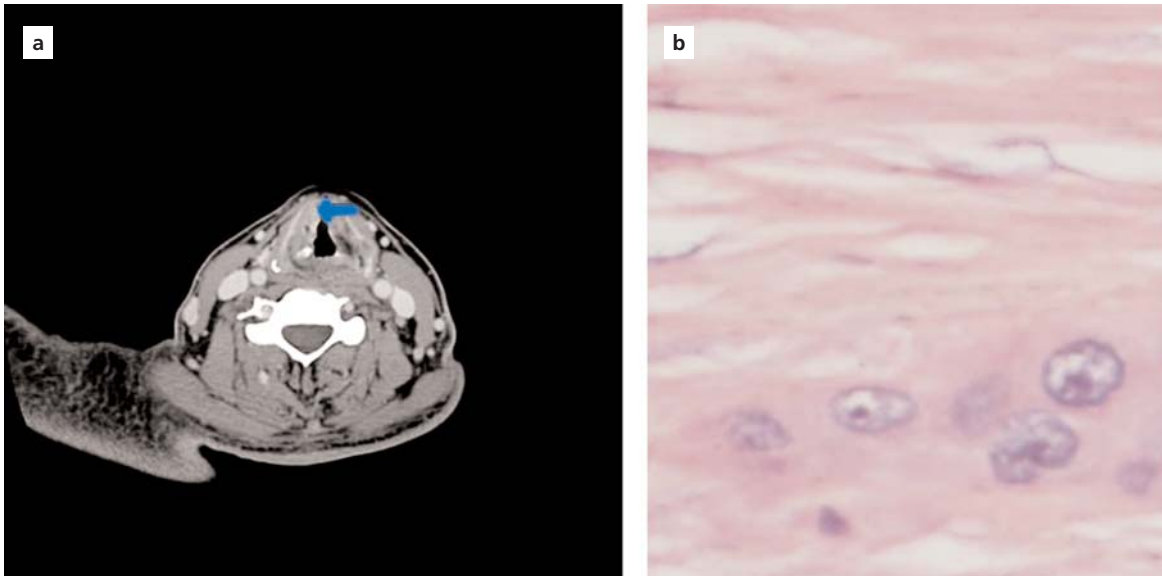
The study retrospectively reviewed 89 patients (stage T4, n=56; stage T3, n=33) who underwent total laryngectomy for treatment of high-grade laryngeal cancer from 2005 to

2013. The study was approved by the local institutional review board. All tumors were reported as squamous cell carcinoma (SCC). Patients with history of preoperative laryngeal surgery or RT were excluded from the study. All of the patients were male with an average age of 67 (range: 48 to 81) years. After a detailed inspection using flexible nasopharyngolaryngoscopy, CT imaging was performed using an Aquilion 64 system (Toshiba, Tokyo, Japan), and 64 sections of the larynx were obtained. Transverse images were obtained (120 kV, 200 mAS, 2-mm section thickness) during normal inspiration after injecting ionizing contrast fluid. All CT images were inspected by a radiologist with 10 years of experience in head and neck radiology, and any suspicion of invasion was accepted as a site of invasion. A pathologist with 10 years of experience in head and neck pathology examined the specimens histopathologically. The total laryngectomy specimens were fixed in formalin and paraffin, cut into 3- to 4- $\mu$ m-thick slices, stained with hematoxylin and eosin, and inspected under light microscopy.

The histopathological results of ELS and invasion of the PES, AC, TC, and SR were compared with the preoperative CT findings (Figs. 1–5). The McNemar test and Z-test were used for the statistical analysis. Data were analyzed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). A p value of <0.05 was accepted as statistically significant.



**Fig. 1.** (a) Contrast-enhanced axial CT imaging of epiglottis with infiltrative tumor, preepiglottic spread (arrow), and (b) its histopathological image (HE  $\times$ 10).

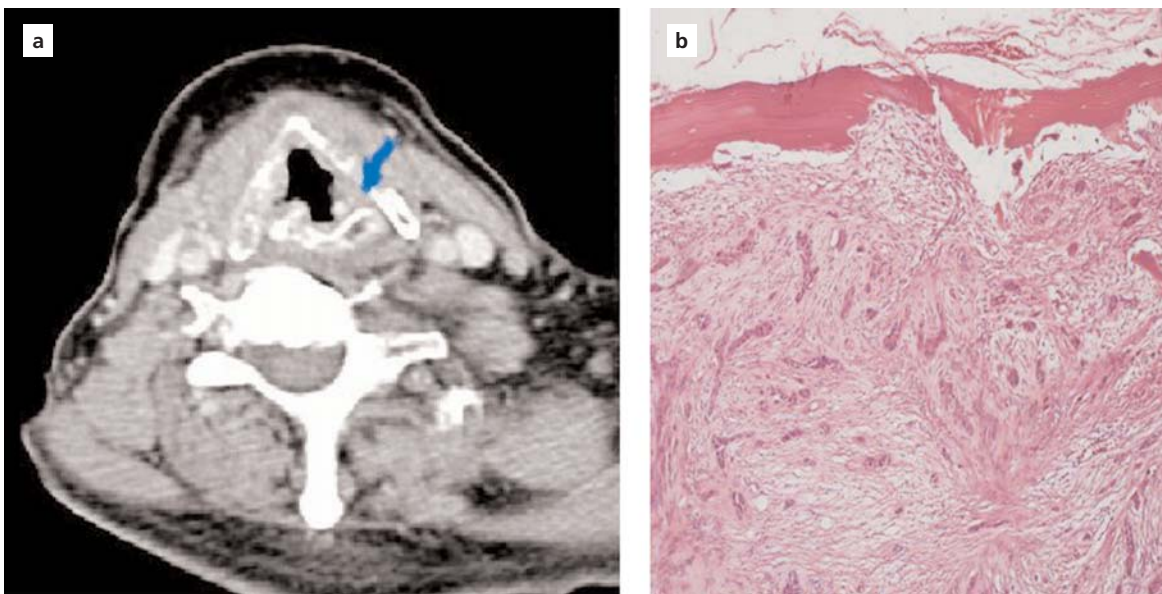


**Fig. 2.** (a) Contrast-enhanced axial CT imaging of a primary tumor located on right vocal cord and anterior commissure (arrow) and (b) its histopathological image (HE x20).

## Results

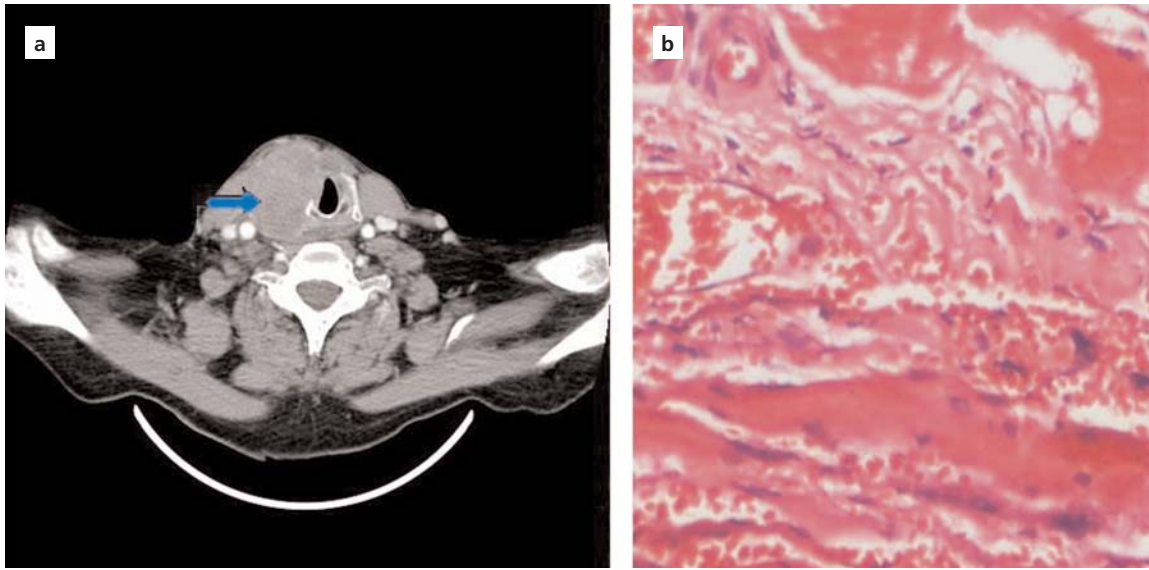
Pre-epiglottic space invasion was found on the preoperative CT images in 41 patients, 5 of whom had negative histopathological findings. The sensitivity, specificity, false-negative, false-positive, and accuracy rates of the CT findings

for PES invasion were 83%, 87%, 16%, 12%, and 85%, respectively (Table 1). SR invasion was seen on CT in 49 patients, 9 of whom had negative histopathological findings; the sensitivity, specificity, false-negative, false-positive, and accuracy rates were 79%, 70%, 15%, 29%, and 79%, respec-



**Fig. 3.** (a) Contrast-enhanced axial CT imaging of thyroid cartilage with invasion especially on the right side and (b) its histopathological image (HE x10).





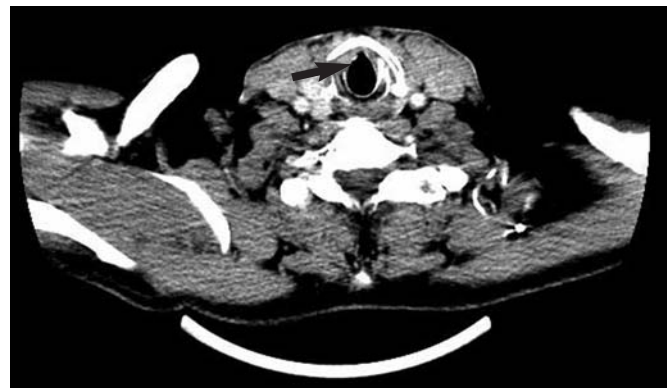
**Fig. 4.** (a) Contrast-enhanced axial CT imaging of extralaryngeal strap muscles with invasion and (b) its histopathological image (HE x10).

tively (Table 2). AC invasion was seen on CT in 38 patients, 15 of whom had negative histopathological findings; the sensitivity, specificity, false-negative, false-positive, and accuracy rates were 69%, 55%, 30%, 44%, and 64%, respectively (Table 3). TC invasion was seen on CT in 28 patients, 16 of whom had negative histopathological findings; the sensitivity, specificity, false-negative, false-positive, and accuracy rates were 84%, 71%, 15%, 28%, and 76%, respectively (Table 4). Finally, ELS was seen on CT in 25 patients, 7 of whom had negative histopathological findings; the sensitivity, specificity, false-negative, false-positive, and accuracy rates were 75%, 87%, 24%, 12%, and 83%, respectively (Table 5).

According to the McNemar test, the difference between the CT findings and histopathological findings was significant only for TC invasion ( $p < 0.05$ ). Given the small sample size, the Z test was used as a second test. This showed that the differences between the CT findings and histopathological findings were significant for ELS and PES, AC, TC, and SR invasion ( $p < 0.05$ ).

### Discussion

More than 90% of laryngeal cancers are SCC. Most cases occur in male smokers 51 to 60 years of age. SCC is classified into three types: infiltrative, bulky, and mixed. SCC may be restricted to the mucosal or submucosal regions, or deep invasion can occur.<sup>[6]</sup> As endoscopic examination has a limited ability to detect submucosal or deep invasion, radiological imaging is often performed. Sometimes, however, radiologi-



**Fig. 5.** Contrast-enhanced axial CT imaging of an early stage primary tumor on the right subglottic region, invasion to this site is observed by the pathologist macroscopically.

**Table 1.** Comparison of preoperative CT and postoperative histopathology in preepiglottic space invasion.

Preoperative CT	Preepiglottic space invasion (histopathologically)						p
	+	%	-	%	Total	%	
+	41	46.06	5	5.61	46	51.68	0.774
-	8	8.98	35	39.32	43	48.31	
Total	49	55.04	40	44.93	89	100	
Sensitivity							83%
Specificity							87%
False (+) value							12%
False (-) value							16%
Accuracy							85%



**Table 2.** Comparison of preoperative CT and postoperative histopathology in subglottic region invasion.

Preoperative CT	Subglottic region invasion (histopathologically)						p
	+	%	-	%	Total	%	
+	49	55.05	9	10.11	58	65.16	1.000
-	9	10.11	22	24.71	31	34.83	
Total	58	65.16	31	34.82	89	100	
Sensitivity							84%
Specificity							70%
False (+) value							29%
False (-) value							15%
Accuracy							79%

cal imaging also fails to reveal the depth of invasion because of the tumor location, radiologist’s interpretation, or imaging device used.<sup>[7]</sup>

The most common site of invasion is the TC (37% of cases), and such invasion most frequently involves the mid-line.<sup>[8]</sup> Once cartilage invasion occurs, the tumor is stage T3 or T4, and the success rate of RT decreases while the risk of recurrence, chondronecrosis, and a nonfunctional larynx after RT increase. In the past, conservative laryngeal surgery was used to manage laryngeal cancer with minimal cartilage invasion. More recently, however, more invasive surgery has been preferred.<sup>[9]</sup> The reported sensitivity and specificity of CT for detecting cartilage invasion range from 46% to 91% and 68% to 94%, respectively.<sup>[10]</sup> Because the TC consists of unmineralized hyaline cartilage, signs of invasion are difficult to detect.<sup>[11]</sup> In this study, the sensitivity, specificity, false-negative, false-positive, and accuracy rates of the preoperative CT findings of cartilage invasion were 83%, 87%, 16%, 12%, and 85%, respectively. These results concur with the

**Table 4.** Comparison of preoperative CT and postoperative histopathology in thyroid cartilage invasion.

Preoperative CT	Thyroid cartilage invasion (histopathologically)						p
	+	%	-	%	Total	%	
+	28	31.46	16	17.97	44	49.43	0.027
-	5	5.61	40	44.94	45	50.56	
Total	33	37.07	56	62.91	89	100	
Sensitivity							84%
Specificity							71%
False (+) value							28%
False (-) value							15%
Accuracy							76%

**Table 3.** Comparison of preoperative CT and postoperative histopathology in anterior commissure invasion.

Preoperative CT	Anterior commissure invasion (histopathologically)						p
	+	%	-	%	Total	%	
+	38	42.69	15	16.85	53	59.55	0.860
-	17	19.10	19	21.34	36	40.44	
Total	55	59.79	34	38.19	89	100	
Sensitivity							69%
Specificity							55%
False (+) value							44%
False (-) value							30%
Accuracy							64%

literature; nevertheless, there was a significant difference in the CT and postoperative histopathological findings of TC invasion.

The PES or Boyer’s space is a triangular region that contains a large amount of fat and small amounts of elastic fibers, collagen fibers, and lymphatic vessels. This space is bordered by the hyoepiglottic ligament superiorly, thyrohyoid membrane and thyroid cartilage anteriorly, and epiglottis and thyroepiglottic ligaments posteriorly.<sup>[12]</sup> Because the epiglottis is a weak barrier, laryngeal cancer can spread to the PES. Once PES invasion occurs, the tumor is stage T3, the prognosis after RT is poorer, and the local metastasis rate increases.<sup>[13]</sup> The reported sensitivity and specificity of CT findings for PES invasion are 86% and 73%, respectively.<sup>[14]</sup> In this study, the sensitivity, specificity, false-negative, false-positive, and accuracy rates of the preoperative CT findings were 84%, 71%, 15%, 28%, and 76%, respectively, which concurs with the literature.

**Table 5.** Comparison of preoperative CT and postoperative histopathology in extralaryngeal invasion.

Preoperative CT	Extralaryngeal invasion (histopathologically)						p
	+	%	-	%	Total	%	
+	25	28.08	7	7.86	53	59.55	0.791
-	8	8.98	49	55.05	36	40.44	
Total	33	37.06	56	62.91	89	100	
Sensitivity							75%
Specificity							87%
False (+) value							12%
False (-) value							24%
Accuracy							83%

The SR is a transition zone between the larynx and trachea, where stratified squamous epithelium changes to respiratory epithelium. Primary cancer of the SR is rare, and most SR cancer occurs as a result of invasion from other parts of the larynx. In the past, a laryngeal tumor at the level of the cricoid cartilage was called SR cancer. The conus elasticus is found between the free border of the vocal cord and upper part of the cricoid cartilage; it serves as a relative barrier, and a tumor may spread laterally and anteriorly to the SR along the conus elasticus. When a tumor invades this membrane, cricoid invasion follows, and the tumor is stage T4.<sup>[15]</sup> Souza et al. reported that the accuracy, sensitivity, and specificity of CT findings for SR invasion were 95.0%, 100.0%, and 93.5%, respectively, while we obtained sensitivity, specificity, false-negative, false-positive, and accuracy rates of preoperative CT findings of 79%, 70%, 15%, 29%, and 79%, respectively.<sup>[16]</sup> Our results are lower than those previously reported, possibly because SR region invasion can be confused with bulging of a tumor.

According to Olofsson, the AC is a small region limited by the anterior angle of the ventricles and is located 2 to 3 mm inferior to the anterior parts of the vocal cords. Tumors in the midline of the laryngeal surface of the epiglottis invade the AC. This results in TC invasion along Broyles' ligament.<sup>[17]</sup> When a tumor is closer than 2 to 3 mm from the AC, conservative surgery to protect the voice is no longer appropriate. With gross tumor invasion of the AC, the reported accuracy of CT was 96.5%.<sup>[18]</sup> In our study, the sensitivity, specificity, false-negative, false-positive, and accuracy rates of the preoperative CT findings were 69%, 55%, 30%, 44%, and 64%, respectively. Our results are lower than reported, possibly because of the poor quality of imaging, high tumor grade, and bulging of the vocal cord tumors.

Extralaryngeal spread can occur in many ways. The tumor can penetrate the cartilage and spread to the strap muscles and anterior and lateral soft tissues. Spread to the anterior soft tissues can follow invasion of the thyrohyoid membrane, pre-epiglottic space, paraglottic space, and constrictive muscles. Spread to the piriform sinus laterally and to the interarytenoid, postcricoid, hypopharynx, and proximal esophagus posteriorly can be seen, as can spread to the cricothyroid membrane and cervical trachea inferiorly. Once such spread occurs, the tumor is deemed stage T4. In one study, the sensitivity and positive predictive value of preoperative CT findings of ELS were 82% and 49%, respectively.<sup>[19]</sup> In our study, the sensitivity, specificity, false-negative, false-positive, and accuracy rates of preoperative CT were 75%, 87%, 15%, 12%, and 76%, respectively, concurring with previously reported values.

## Conclusion

Our study is first reported in the literature that evaluated all of the critical regions for the total or partial laryngectomy on computed tomography in advanced laryngeal cancer. Statistical analysis showed that preoperative CT imaging does not provide dependable information about ELS or invasion of the PES, AC, TC, or SR. Consequently, these regions are potential preoperative traps. Tumor invasion to these regions affects patient management and should thus be assessed during surgery using frozen section analysis.

**Conflict of Interest:** No conflicts declared.

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# New diagnostic indicators in chronic otitis media with effusion: neutrophil to lymphocyte ratio and thrombocyte lymphocyte ratio

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## Abstract

**Objective:** Inflammation has an important place in chronic otitis media with effusion (COME) etiology. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are simple and cheap tests that show inflammation and can be calculated by all physicians. In our study, we aimed to investigate the relationship between COME and NLR and PLR parameters.

**Methods:** The study was performed with the pediatric patient group consisting of 77 patients who got diagnosis of COME and the control group consisting of 62 healthy children whose age, gender and demographical characteristics were concordant with the patient group. The patient and control groups were compared statistically in terms of NLR and PLR values.

**Results:** Mean neutrophil to lymphocyte ratio value was found as  $1.43 \pm 0.54$  in the patient group and as  $1.16 \pm 0.51$  in the control group ( $p < 0.001$ ). Mean PLR value was found as  $113.78 \pm 35.78$  in the patient group and as  $103.61 \pm 32.32$  in the control group ( $p = 0.084$ ).

**Conclusion:** Neutrophil to lymphocyte ratio and PLR values were high in COME. It was shown for the first time that NLR can be used as a diagnostic parameter in children with COME.

**Keywords:** Serous otitis media, inflammation, neutrophil, lymphocyte, thrombocyte.

## Özet: Kronik effüzyonlu otit tanısında yeni tanısal belirteçler: Nötrofil lenfosit oranı ve trombosit lenfosit oranı

**Amaç:** Enflamasyon, kronik effüzyonlu otit (KEOM) etyolojisinde önemli bir yere sahiptir. *Neutrophil to lymphocyte ratio* (NLR) ve *platelet to lymphocyte ratio* (PLR) enflamasyonu gösteren ve bütün hekimlerin hesaplayabileceği basit, ucuz testlerdir. Bu çalışmada KEOM ile NLR ve PLR değerleri arasındaki ilişkiyi ortaya koymayı amaçladık.

**Yöntem:** Çalışma KEOM tanısı konmuş olan 77 hastadan oluşan çocuk hasta grubu ile yaş, cinsiyet ve demografik özellikleri hasta grubu ile uyumlu 62 sağlıklı çocuktan oluşan kontrol grubu ile yapıldı. Hasta ve kontrol grubu, NLR ve PLR değerleri açısından istatistiksel olarak karşılaştırıldı.

**Bulgular:** Hasta grubunda NLR değeri ortalaması  $1.43 \pm 0.54$ , kontrol grubunda NLR ortalama değeri  $1.16 \pm 0.51$  olarak bulundu ( $p < 0.001$ ). PLR değeri ortalaması hasta grubunda  $113.78 \pm 35.78$ , kontrol grubunda  $103.61 \pm 32.32$  olarak saptandı ( $p = 0.084$ ).

**Sonuç:** Kronik effüzyonlu otitte NLR ve PLR değerleri yüksek bulunmuştur. KEOM tanısı olan çocuklarda NLR'nin tanıma yardımcı parametre olarak kullanılabilmesi literatürde ilk kez gösterilmiştir.

**Anahtar sözcükler:** Seröz otitis media, enflamasyon, nötrofil, lenfosit, trombosit.

Otitis media with effusion (OME) is the liquid in the middle ear cavity without having findings of inflammation or infection. OME is one of the most frequent hearing losses in childhood period. Thus, it affects language and cognitive development of the children in case it is not treated.<sup>[1]</sup>

OME continues more than three months in some cases despite of medical treatment and called chronic otitis media with effusion (COME). Adhesive otitis media, chronic otitis media and cholesteatoma may develop in time depending on COME.<sup>[2]</sup> Thus, the follow up of the

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patient should not be prolonged; a ventilation tube should be installed.

Complete blood count (CBC) analysis was made in blood sample that was taken from peripheral vein in order to determine neutrophil to lymphocyte ratio (NLR) and also platelet to lymphocyte ratio (PLR). PLR was found to be high in several peripheral vascular diseases, coronary artery diseases and some gynecological and hepatobiliary malignities and was associated with poor prognosis. NLR may increase in systemic inflammation, some gynecological and gastrointestinal cancers and some cardiovascular diseases.<sup>[3,4]</sup>

It was shown in the study performed by Somuk et al.<sup>[5]</sup> that mean platelet volume (MPV) parameter could be used as an auxiliary parameter in diagnosing in the children with COME. In our study, the research was to diagnose children with COME.

## Materials and Methods

### Patients and subject

Ventilation tube was applied to seventy-seven patients with COME between January 2013 and June 2014. The control group consisted of 62 healthy children that are similar with the patient group in terms of age, gender and demographic characteristics.

In patient group, children who were determined to have otitis media with effusion via otoscopic examination, conductive hearing loss in audiological evaluation and type B tympanogram were included.

The patients who were under six years old were followed via anti-inflammatory treatment and short time (three days) topical decongestant treatment. The patients who were over six years old were followed via anti-inflammatory treatment and systemic decongestant treatment quarterly. Ventilation tube was applied to the patients who could not respond to the treatment and continued to have otitis media with effusion in otoscopic treatment and audiological evaluation at the end of three months.

Hemogram analysis was made in blood sample that was taken from the peripheral vein. In the patient and control group, children who with chronic adenotonsillar disease, chronic inflammatory disease, active upper respiratory tract infection, asthma, allergic rhinitis, chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, immune disorder, metabolic disease and cystic fibrosis were excluded from the study.

Complete blood count was determined (Sysmex WE-2100; Sysmex, Mundelein, IL, USA) and based on mean platelet volume (MPV), erythrocyte, leukocyte, neu-

trophil, lymphocyte and thrombocyte counts were used to determine PLR and NLR. NLR value was calculated by dividing neutrophil number into lymphocyte number and PLR value was calculated by dividing thrombocyte number into the lymphocyte number. Leukocyte, neutrophil, lymphocyte, thrombocyte, MPV, NLR and PLR values of the patient and control group were compared to each other statistically.

### Statistical analysis

Descriptive statistics were presented as mean  $\pm$  standard deviation, and the categorical variables were presented as the number of the cases and %. The comparison of the difference for age, gender and complete blood count parameters between patient and control group was tested using t-test.  $P < 0.05$  value was considered significant. Statistical Package Program for Social Sciences (SPSS) for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

## Results

While there were 47 male and 30 female children in the patient group, there were 34 male and 28 female children in the control group. While the mean age of the patient group was  $7.06 \pm 2.67$  (range: 3 to 15), the mean age of the control group was found as  $7.77 \pm 2.84$  (range: 4 to 15). It was determined in the statistical evaluation that patient and control group were similar with each other in terms of age and gender (Table 1).

Mean neutrophil value in the patient group was found as  $4.17 \pm 1.37$  and it was found as  $3.55 \pm 1.50$  in the control group ( $p=0.012$ ). Neutrophil number in the patient group was significantly and statistically higher than the control group.

Mean leukocyte value in the patient group was found as  $8.06 \pm 2.03$  and this value was found as  $7.68 \pm 2.12$  in the control group ( $p=0.283$ ). While mean thrombocyte value was  $323.75 \pm 59.46$  in the patient group, it was found as  $312.54 \pm 57.35$  in the control group ( $p=0.264$ ). While mean MPV value was  $9.37 \pm 1.42$  in the patient group, it was

**Table 1.** Patients' age and gender distribution.

		Patient group	Control group	p value
Age		$7.06 \pm 2.67$	$7.77 \pm 2.84$	0.133
Gender	Male	47 (61%)	34 (55%)	0.465
	Female	30 (39%)	28 (45%)	



found as  $9.12 \pm 1.10$  in the control group ( $p=0.247$ ). Leukocyte, thrombocyte and MPV parameters were high in the patient group; however, the change was not statistically significant.

Mean lymphocyte value in the patient group was found as  $3.03 \pm 0.82$  and it was  $3.28 \pm 1.14$  in the control group ( $p=0.146$ ). Lymphocyte number was lower in the patient group; however, the change was not statistically significant (Table 2).

While mean NLR value in the patient group was  $1.43 \pm 0.54$ , it was found as  $1.16 \pm 0.51$  in the control group and the change was statistically significant ( $p < 0.001$ ). While mean PLR value in the patient group was found as  $113.78 \pm 35.78$  and it was found as  $103.61 \pm 32.32$  in the control group; however, the change was not statistically significant ( $p=0.084$ ) (Table 2).

## Discussion

Currently, COME is one of the most important health problem in children. COME prevalence varies much and it changes between 1.3–31.3%.<sup>[6,7]</sup> In the comprehensive study that was performed by Erdivanli et al.<sup>[8]</sup> COME prevalence was found as 9.9% in Turkey.

In COME etiology, there are viral or bacterial infections, Eustachian tube dysfunction, allergy and gastroesophageal reflux. There are studies that emphasize importance of the inflammation in COME etiopathogenesis. In the study that was performed by Yellon et al.,<sup>[9]</sup> it was found that interleukin-1-beta, interleukin-2, tumor necrosis factor-alpha and gamma-interferon cytokines are high in children with COME.

Smirnova et al.<sup>[10]</sup> determined in children with COME that pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin-1-beta, interleukin-6 and interleukin-8) and arachidonic acid metabolites are high.

**Table 2.** Patients' complete blood count parameters.

	Patient group	Control group	p-value
NLR	$1.43 \pm 0.54$	$1.16 \pm 0.51$	$< 0.001$
PLR	$113.78 \pm 35.78$	$103.61 \pm 32.32$	0.084
WBC	$8.06 \pm 2.03$	$7.68 \pm 2.12$	0.283
Neutrophil	$4.17 \pm 1.37$	$3.55 \pm 1.50$	0.012
Lymphocyte	$3.03 \pm 0.82$	$3.28 \pm 1.14$	0.146
Platelet	$323.75 \pm 59.46$	$312.54 \pm 57.35$	0.264
MPV	$9.37 \pm 1.42$	$9.12 \pm 1.10$	0.247

MPV: Mean platelet volume; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; WBC: leukocyte

In the study performed by Somuk et al.<sup>[5]</sup> MPV parameter that is an inflammatory marker was examined preoperatively in the children with chronic effusion otitis media. MPV parameter was found high in the children with COME. Our study was performed with larger number of patient and control group. In our study, MPV parameter was found similarly high in the children with COME; however, the change was not statistically significant.

NLR and PLR values are the tests that can be calculated easily and that are quite cost-efficient. It was proposed that NLR is used as a new marker showing systemic inflammation. It was shown that NLR value might assist for determining short- and long-term mortality in acute coronary syndrome. Mortality increased in the patients having high NLR value.<sup>[11]</sup> Sudden sensorineural hearing loss is one of the emergencies of the otorhinolaryngology and inflammation in the etiopathogenesis has an important place. In the study performed by Ulu et al., NLR value was higher than the control group in the patients having sudden hearing loss. In the same study, there was a decrease in response to the treatment in the patients whose NLR value was high and this was stated as bad prognostic factor.<sup>[12]</sup> In the English literature, no study that investigated NLR as a diagnostic parameter in COME was encountered.

In our study, NLR value was found as statistically and significantly higher than the control group in similar age and gender distribution in the pediatric patients to whom ventilation tube was applied because of COME. NLR value, which is used as an inflammatory indicator, can be used in diagnosing the patients with COME.

Like NLR value, PLR value is an inflammatory marker that shows chronic inflammation, is cheap and does not necessitate additional cost. In the study performed by Azab et al. on 619 patients with non-ST-elevation myocardial infarction, it was shown that high PLR value increases the mortality rate.<sup>[13]</sup> In the English literature, no study that investigated PLR as a diagnostic parameter in COME was encountered. In our study, PLR parameter was found to be high in the children with COME; however, the change was not statistically significant.

## Conclusion

NLR value was statistically and significantly higher in the patients with COME. In COME diagnosis, NLR value can be used as the tests, which can be calculated easily, are cheap and that give fast results.

**Conflict of Interest:** No conflicts declared.

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# The relationship between clinical and laboratory findings and duration of sleep where oxygen saturation remains below 90–95% in obstructive sleep apnea

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## Abstract

**Objective:** The aim of the present study was to determine correlations between CT<sub>90</sub> and CT<sub>95</sub> values and physical examination parameters, chronic metabolic diseases, smoking, mean platelet volume, cerebral magnetic resonance imaging (MRI), presence and number of hyperintense foci in obstructive sleep apnea (OSA).

**Methods:** A total of 1154 patients who underwent polysomnography in our sleep laboratory between 2011 and 2014 were screened retrospectively. Among them, 72 cases who underwent ear, nose and throat examinations, cerebral MR, CBC and biochemical tests were included in the study. All patients underwent a detailed anamnesis together with (1) measurements of BMI (body mass index) (2) circumferences of neck and abdomen, (3) examination of oropharynx, (4) Müller maneuver with the aid of fiberoptic endoscope, (5) estimation of Epworth sleep scale scores, (6) and polysomnographic (PSG) tests.

**Results:** According to the severity of OSA, the patients had simple snoring (22.2%), mild (19.4%) and severe OSA (38.9%). In multivariate regression analysis, body mass index (BMI) (p=0.026) and apnea/hypopnea index (AHI) (p=0.013) were seen as independent variables affecting CT<sub>90</sub> (R<sup>2</sup>=49%). Multivariate linear regression analysis demonstrated that independent variables of smoking (p=0.001), AHI (p= 0.003) and number of hyperintense foci (p=0.013) affected CT<sub>95</sub> (R<sup>2</sup>=%47.9), while relationships between diabetes, BMI and CT<sub>95</sub> were not statistically significant.

**Conclusion:** Since CT<sub>95</sub> values are affected by smoking without any statistically significant correlation with retropalatal and retroglossal Müller stages, we think that consideration of CT<sub>90</sub> value will be more appropriate in the evaluation of the severity of chronic intermittent hypoxia in patients with obstructive sleep apnea. However, the correlation between CT<sub>90</sub> value and AHI is closer to the value indicated in the literature, but not stronger.

**Keywords:** Obstructive sleep apnea, duration of sleep, clinical, laboratory.

## Özet: Obstrüktif uyku apnesinde oksijen saturasyonunun %90-95 altında kaldığı durumlarda uyku süresi ile klinik ve laboratuvar bulguları arasındaki ilişki

**Amaç:** Bu çalışmanın amacı obstrüktif uyku apnesinde (OUA); CT<sub>90</sub> ve CT<sub>95</sub> değerleri ile fizik muayene parametreleri, kronik metabolik hastalıklar, sigara içimi, ortalama trombosit hacmi, beyin manyetik rezonans görüntülemesinde (MRG) hiperintens odak varlığı ve sayısı arasındaki ilişkileri saptamaktır.

**Yöntem:** Hastanemiz uyku laboratuvarında 2011–2014 tarihleri arasında polisomnografi uygulanan 1154 olgu retrospektif olarak tarandı. Bu hastalardan kulak burun boğaz muayenesi yapılmış, beyin MRG, CBC ve biyokimya tetkikleri bulunan 72 olgu çalışmaya dahil edildi. Tüm hastalarda ayrıntılı anamnez ile birlikte (1) Vücut kitle indeksi (VKİ), (2) boyun ve karın çevresi ölçümü, (3) orofarenks muayenesi, (4) fiberoptik endoskop ile Müller manevrası uygulaması, (5) Epworth uyku skalası ve (6) polisomnografi (PSG) tetkikleri yapıldı.

**Bulgular:** Olguların OUA şiddetine göre dağılımı: %22.2 basit horlama, %19.4 hafif, %19.4 orta ve %38.9 ağır OUA idi. Çoklu doğrusal regresyon analizi yapıldığında apne-hipopne indeksi (AHI) (p=0.026) ve vücut kitle indeksinin (VKİ) (p=0.013) CT<sub>90</sub>'i etkileyen bağımsız değişkenler olduğu (R<sup>2</sup>=%49) görüldü. Çoklu doğrusal regresyon analizi yapıldığında sigara içimi (p=0.001), AHI (p=0.003) ve hiperintens odak sayısının (p=0.013) CT<sub>95</sub>'i etkileyen bağımsız değişkenler olduğu (R<sup>2</sup>=%47.9), diyabet ve VKİ ile CT<sub>95</sub> ilişkisinin istatistiksel olarak anlamlı olmadığı görüldü.

**Sonuç:** CT<sub>95</sub> değerinin sigara içiminden etkileniyor olması, ancak retro-palatal ve retroglossal Müller evreleri ile istatistiksel anlamlı ilişkisi bulunmaması nedeniyle, obstrüktif uyku apnelilerde kronik entermitan hipoksi şiddetinin değerlendirilmesinde CT<sub>90</sub> değerinin dikkate alınmasının daha uygun olduğu düşünülmüştür. Bununla birlikte CT<sub>90</sub> değerinin AHI ile korelasyonu CT<sub>90</sub> için literatürde belirtilen değere yakın, ancak daha güçlüdür.

**Anahtar sözcükler:** Obstrüktif uyku apnesi, uyku süresi, klinik, laboratuvar.

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Obstructive sleep apnea (OSA) is a prevalently seen syndrome characterized by recurrent collapses and intermittent hypoxia of upper respiratory tract. Impairment of gas exchange leads to oxygen desaturation, hypercapnia and fragmentation of sleep with resultant metabolic, neurocognitive and cardiovascular disorders.<sup>[1]</sup> Apnea/hypopnea index (AHI) is used in the determination of the severity of OSA; however, AHI does not provide information about the duration of apnea and its morphology.<sup>[2]</sup> Whereas, the longer the apneic episodes persist, the deeper is the hypoxia. Therefore, AHI does not fully reflect pathophysiologic characteristics of hypoxia.<sup>[3]</sup> Cases with similar AHI values may have different clinical symptoms and sign.<sup>[4,5]</sup> Chronic intermittent type is generally described as recurrent hypoxemic attacks followed by periodic reoxygenation.<sup>[6]</sup> Nowadays, a globally accepted quantitative clinical test which can be used in the measurement of the severity of hypoxia does not exist.<sup>[1]</sup>

In recent years, due to a direct correlation between  $ST_{90}$  value, severity and duration of hypoxia, OSA has attracted gradually increasing attention in investigations performed on OSA.<sup>[7-9]</sup> Bostanci et al. investigated the relationship between various polysomnographic parameters and  $ST_{90}$  and reported age, body mass index (BMI), male gender, AHI, mean oxygen saturation as independent variables affecting  $ST_{90}$ .<sup>[1]</sup> They indicated that AHI and  $ST_{90}$  values should be evaluated in combination as an appropriate approach to the determination of prognosis of the disease and selection of suitable treatment modality for the patient. In this study, the ratio between total of sleep durations where oxygen saturations stayed below 90, and 95% and total duration of sleep was determined as  $CT_{90}$  and  $CT_{95}$  values, respectively. Since these values represent the ratio between the time passed at the hypoxic state and total duration of sleep, they are considered to be a better indicator than  $ST_{90}$  values.

The aim of the present study was to determine correlations between physical examination parameters, chronic metabolic diseases, smoking, mean platelet volume, cerebral magnetic resonance imaging (MRI), presence and number of hyperintense foci.

## Materials and Methods

A total of 1154 patients who underwent polysomnography in our sleep laboratory between 2011 and 2014 were screened retrospectively. Among them, those who underwent ear, nose and throat examinations, cerebral MR, CBC and biochemical tests were included in the study.

All patients underwent a detailed anamnesis together with (1) measurements of BMI, (2) circumferences of neck and abdomen, (3) examination of oropharynx, (4) Müller maneuver with the aid of fiberoptic endoscope, (5) estimation of Epworth sleep scale scores, (6) and polysomnographic (PSG) tests. Hypertension, other cardiovascular diseases, diabetes, and smoking habits were questioned. Tonsil size was graded. The patients were requested to open their mouths with their tongues remaining in their mouths. Oral cavity was inspected, and the position of the palate and root of the tongue was evaluated and modified Malampati score was determined. All patients were subjected to Müller maneuvers while seated and degree of obstruction at the level of the soft palate and tongue root was assessed. For the assessment of an upper respiratory tract of a patient seated erect, a fiberoptic endoscope was inserted through nasal route complying with the Frankfurt line parallel to the ground. Fibroscope was advanced till epiglottis was visible. During Müller maneuver (forced inspiration with the closed mouth and nose) retropalatal and retroglottal regions were observed. Müller maneuvers were repeated three or more times in case of need till we were certain that the patient made a forceful inspiration. The degree of retropalatal and retroglottal collapse was staged (Table 1).

Patients with chronic renal, heart or liver failure, abnormal pulmonary functions or sleep disorders other than OSA and patients who experienced previously any surgical intervention or those using any respiratory device for their treatment were not included in the study.

All patients underwent all-night polysomnographic examination in the Sleep Laboratory of Chest Diseases, Alanya Hospital of Başkent University using 44-channel Compumedics brand E series (Abbotsford, Australia) computerized system under the surveillance of an experienced technician. Polysomnographic examinations included (EEG), 2-channel electro-oculography (EOG), single-channel submental muscle electromyography (EMG), 2-channel EMG whose electrodes were placed on both anterior tibial muscles, 1-channel nasal cannula for the measurement of oronasal airflow, 1-channel oronasal thermal sensor, 2-channel inductive plethysmography to display respiratory efforts of thorax, and abdomen, “body position” sensor to determine position of the body, pulse oximetry device with a single-channel finger probe to measure arterial oxyhemoglobin ( $SpO_2$ ) concentration and simultaneous video recordings. Apnea was defined as cessation of respiration for  $\geq 10$  seconds. At least 50% drop in respiratory effort together with 4% drop in  $SaO_2$  was considered as hypopnea. AHI is the number of apneas and hypopneas per hour (Table 1).

### Statistical analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v21 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using Shapiro-Wilk test. Parametric tests (independent-samples t-test and posthoc Tukey test) were applied to data of normal distribution and non-parametric tests (Mann-Whiney U test and Kruskal-Wallis test) were applied to data of

**Table 1.** Staging system of polysomnographic and physical examination findings used in patients evaluated for OSA.

Parameter	Stage	Description
Apnea hipopnea index (AHI)	1 (primary snoring)	AHI ≤ 5
	2 (mild)	5 < AHI ≤ 15
	3 (moderate)	15 < AHI ≤ 30
	4 (severe)	>30
Body mass index (BMI) (kg/m <sup>2</sup> )	1	<25
	2	25 ≤ BMI ≤ 30
	3	30 < BMI ≤ 40
	4	>40
Size of the tonsils	0	Tonsillectomized
	1	Tonsils are in the tonsillar fossa, lateral to the plicae
	2	Occupies 25–50% of oropharynx
	3	Occupies 50–75% of oropharynx
Modified Mallampati	4	Occupies >75% of oropharynx; it nearly joins at midline
	1	Soft palate, plicae and tonsils can be seen
	2	Uvula, plicae and upper poles of tonsils can be seen
	3	Soft palate can be partially seen
Retropalatal Müller stage	4	Only hard palate is visible
	1	Less than 25 collapse of pharyngeal walls during Müller maneuver
	2	25–50%
	3	50–75%
Retroglossal Müller stage	4	>75%
	1	Vallecula and vocal cords are completely visible
	2	Vallecula and vocal cords are partially visible
	3	Root of the tongue touches epiglottis, and arythenoids are visible
	4	Root of the tongue pushes epiglottis and arythenoids cannot be seen.

questionably normal distribution. To calculate correlation coefficients, Spearman correlation was used. Data are expressed as mean±SD or median (interquartile range), as appropriate. Statistical significance was considered as p<0.05.

### Results

General characteristics of the patients are seen in Table 2. The mean age of the patients was 47.6±12.2 (range: 23 to 75) years. The study population consisted of 64 (88.9%) male and 8 (11.1%) female patients. According to severity of OSA, the patients had simple snoring (22.2%), mild (19.4%) and severe OSA (38.9%).

Based on Spearman correlation analysis CT<sub>90</sub> was correlated with Epworth sleep score (r=0.29, p=0.013), AHI (r=0.713, p<0.001) and BMI (r=0.549, p<0.001). However, variables of diabetes mellitus (p=0.040), retropalatal Müller stage (p=0.018) and retroglossal Müller stage (p=0.034) affected CT<sub>90</sub> (Table 3). However, in multivariate regression analysis only BMI (p=0.026) and AHI (p=0.013) were

**Table 2.** General characteristics of the patients (n=72).

		mean±SD	min-max
CT <sub>90</sub> , %		7.16±14.68	0–75.6
CT <sub>95</sub> , %		44.6±31.57	0–100
Epworth sleep score		9.13±5.18	0–24
Hemoglobin (g/dL)		14.43±1.29	10.2–17.1
Mean platelet volume (fl)		7.86±1.51	5–15.3
Apnea hypopnea index		28.15±24.84	0–93
Body mass index (kg/m <sup>2</sup> )		31.12±5.33	21.9–48
		n	%
Hyperintense foci	Absent	38	52.8
	Present	34	47.2
Number of hyperintense foci	Absent	34	47.2
	1–4	16	22.2
	≥5	22	30.6
Hypertension	Absent	40	55.6
	Present	32	44.4
Diabetes	Absent	58	80.6
	Present	14	19.4
Cardiovascular disease	Absent	59	81.9
	Present	13	18.1
Hyperlipidemia	Absent	54	75.0
	Present	18	25.0
Smoking	Absent	46	63.9
	Present	26	36.1



seen as independent variables affecting CT<sub>90</sub> (R<sup>2</sup>=49%) (Table 4). Spearman correlation analysis revealed correlation between CT<sub>95</sub> and AHI (r=0.604, p<0.001) and BMI (r=0.473, p<0.001). However, variables of diabetes (p=0.005), smoking (p=0.017) and number of hyperintense foci (p=0.011) affected CT<sub>95</sub> (Table 3). Multivariate linear regression analysis demonstrated that independent variables of only smoking (p=0.001), AHI (p=0.003) and number of hyperintense foci (p=0.013) affected CT<sub>95</sub> (R<sup>2</sup>=47.9%), while relationships between diabetes, BMI and CT<sub>95</sub> were not statistically significant (Table 4).

### Discussion

The total duration of sleep where oxygen saturation remains below 90% and 95%, is an easily measurable

objective parameter. In this study a statistically significant correlation was not detected between retropalatal Müller stage, retroglossal Müller stage and CT<sub>95</sub> values, However, correlations between retropalatal Müller stage and retroglossal Müller stage CT<sub>90</sub> values were seen (p=0.018 and p=0.034, respectively).

Li and Jin reported a strong correlation between AHI and total duration of apnea (r=0.770 and 0.776, respectively).<sup>[7]</sup> In our study, a strong correlation was found between CT<sub>90</sub> value and AHI; however, it was not so strong as ST<sub>90</sub> value indicated in the study by Li and Jin. (r=0.0713). A moderate degree of correlation was found between CT<sub>95</sub> and AHI (r=0.604). Besides, a correlation between Epworth sleep score and CT<sub>90</sub> (r=0.290) was found, whereas, a statistically significant correlation was not detected between CT<sub>95</sub> and EUS.

**Table 3.** Factors affecting CT<sub>90</sub> and CT<sub>95</sub>.

		CT <sub>90</sub>		CT <sub>95</sub>	
		Median [min–max]	p value	Median [min–max]	p value
Hyperintense foci	Absent	0.40 [0–75.63]	0.364	31.7 [0.04–100]	0.146
	Present	1.11 [0–41.02]		48.6 [2.86–92.21]	
Hypertension	Absent	0.61 [0–48.66]	0.692	36.4 [0.04–96.61]	0.362
	Present	0.78 [0–75.63]		44.1 [1.63–100]	
Diabetes	Absent	0.40 [0–48.66]	0.040	30.0 [0.04–100]	0.005
	Present	4.46 [0–75.63]		74.3 [12.3–92.6]	
Cardiovascular	Absent	0.64 [0–75.63]	0.482	42.3 [0.04–100]	0.703
	Present	0.32 [0–41.02]		43.4 [1.63–86.3]	
Hyperlipidemia	Absent	0.61 [0–75.63]	0.696	41.4 [0.04–96.61]	0.830
	Present	1.04 [0–60.58]		51.5 [1.63–100]	
Smoking	Absent	0.31 [0–60.58]	0.088	28.0 [0.04–89.2]	0.017
	Present	2.21 [0.01–75.63]		63.9 [1.12–100]	
Gender	Male	0.71 [0–75.63]	0.405	44.9 [0.04–100]	0.333
	Female	0.27 [0–33.16]		22.2 [0.05–92.12]	
Number of hyperintense foci	WML absent	0.40 [0–75.63]	0.319	31.7 [0.04–100]	0.011
	WML 1–4	0.42 [0–33.16]		24.3 [0.13–91.85]	
	WML >5	1.72 [0.05–41.02]		62.4 [12.91–92.21]	
Mallampati stage	1	0.25 [0.01–33.16]	0.276	43.4 [0.05–92.12]	0.169
	2	0.46 [0–41.02]		29.5 [0.13–100]	
	3-4	0.85 [0–75.63]		65.0 [0.04–92.63]	
Tonsillar stage	1-2	0.30 [0–60.58]	0.128	30.9 [0.04–92.21]	0.213
	3	0.91 [0–75.63]		46.4 [1.63–100]	
	4	7.34 [0.09–19.14]		53.6 [26.9–86.3]	
Retropalatal Müller stage	1	0.17 [0–6.51]	0.018	20.3 [0.05–91.85]	0.063
	2	0.27 [0–33.16]		26.1 [0.13–96.61]	
	3	1.80 [0.04–60.58]		54.8 [6.93–92.21]	
	4	6.11 [0–75.63]		60.2 [0.04–100]	
Retroglossal Müller stage	1	0.62 [0–41.02]	0.034	35.6 [1.63–100]	0.072
	2	0.32 [0–36.29]		32.8 [0.04–96.61]	
	3-4	17.1 [0.05–75.63]		79.5 [9.96–92.63]	

Recent studies have demonstrated the close relationship between obesity and OSA, insulin resistance and metabolic syndrome.<sup>[10,11]</sup> The studies performed more recently have detected that metabolic dysfunction developed in OSA which is not only correlated with obesity but also related closely to the severity of OSA irrespective of the presence of obesity.<sup>[12,13]</sup> Punjabi et al. demonstrated that the insulin resistance developed in patients with OSA increases in parallel with the increase in the severity of the disease and pointed out to the severity of oxygen desaturation as one of the important factors which increase the insulin resistance.<sup>[14,15]</sup> In our study, CT<sub>90</sub> and CT<sub>95</sub> values were found to be correlated with the presence of diabetes (p=0.040 and p=0.005, respectively).

In obstructive sleep apnea, hyperintense foci (= alterations in white matter) on cerebral periventricular and subcortical areas at T2-weighted and FLAIR (fluid attenuated inversion recovery) sequences of magnetic resonance imaging in obstructive sleep apnea were found to be correlated with, dementia and mortality.<sup>[16-18]</sup> They are related to cognitive function and their preventable and treatable causes should be revealed.<sup>[19,20]</sup> Even though heterogeneous pathological relations exist, the presence of gliosis related to focal myelinosis, axonal loss and hyalinosis suggests a role of chronic hypoperfusion in the development of hyperintense foci.<sup>[21,22]</sup> Obstructive sleep apnea is related to the development of hypertension and hypertension was correlated with the development of hyperintense foci.<sup>[16,23,24]</sup> Therefore, the presence of a cor-

relation between OSA and the presence of hyperintense foci is reasonable.<sup>[25]</sup> In this study, a correlation between CT<sub>90</sub> value and the presence of hyperintense foci in the brain could not be found. However, a correlation was found between CT<sub>95</sub> value and number of hyperintense foci in the brain (p=0.011).

Increased activation of platelets plays an important role in the development of cardiovascular complications.<sup>[26]</sup> Some authors have indicated an increase in platelet activation and aggregation.<sup>[27-30]</sup> Mean platelet volume is an indicator of thrombocytic activation and plays a role in the pathophysiology of cardiovascular diseases as hypertension, diabetes, hypercholesterolemia and acute myocardial infarction.<sup>[26,31]</sup> In this study, a statistically significant correlation was not detected between mean platelet volume, CT<sub>90</sub> and CT<sub>95</sub> values. Besides, statistically significant effect of smoking on CT<sub>95</sub> (p=0.017) was seen; however, it did not affect CT<sub>90</sub> values.

Polysomnographic, brain MR and blood values obtained at different time points because of retrospective design of the study and a scarce number of cases are major limitations of our study. Besides among cases who had undergone polysomnographic examinations, selection of only those who had cerebral MR and biochemical values might create a bias towards the cases who had health problems apart from OSA.

Based on the results of this study, correlations exist between CT<sub>90</sub> value, AHI, BMI, Epworth sleep score,

**Table 4.** Factors affecting CT<sub>90</sub> and CT<sub>95</sub> (multivariate linear regression analysis).

		Regression coefficient (95% confidence interval)	p value	R <sup>2</sup>
CT <sub>90</sub>	Retroplatal Müller stage	0.419 (-2.58-3.419)	0.781	49%
	Retroglossal Müller stage	3.659 (-0.501-7.818)	0.084	
	Smoking	-0.049 (-5.719-5.621)	0.986	
	Diabetes	1.440 (-6.331-9.211)	0.712	
	Apnea hipopnea index	0.384 (-0.168-0.936)	0.169	
	Body mass index	0.173 (0.022-0.323)	0.026	
	Number of hyperintense foci	0.834 (0.180-1.488)	0.013	
CT <sub>95</sub>	Retroplatal Müller stage	1.546 (-5.041-8.133)	0.641	47.9%
	Retroglossal Müller stage	-5.783 (-14.873-3.307)	0.208	
	Smoking	21.198 (8.906-33.490)	0.001	
	Diabetes	6.337 (-10.440-23.114)	0.453	
	Apnea hipopnea index	0.504 (0.178-0.830)	0.003	
	Body mass index	1.052 (-0.334-2.439)	0.134	
	Number of hyperintense foci	8.615 (1.855-15.376)	0.013	

retropalatal, retroglossal stage and presence of diabetes. On the other hand, CT<sub>95</sub> value is correlated with AHI, BMI, diabetes, smoking and number of hyperintense foci detected on brain MR. In multivariate linear regression analysis, CT<sub>90</sub> value was correlated with only AHI and BMI and CT<sub>95</sub> value was correlated with AHI, smoking and a number of hyperintense foci in the brain. Since CT<sub>95</sub> values are affected by smoking without any statistically significant correlation with retropalatal and retroglossal Müller stages, we think that consideration of CT<sub>90</sub> value will be more appropriate in the evaluation of the severity of chronic intermittent hypoxia in patients with obstructive sleep apnea. However, the correlation between CT<sub>90</sub> value and AHI is closer to the value indicated in the literature, but not stronger.

**Conflict of Interest:** No conflicts declared.

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# The influence of iris color and retina pigment epithelium melanin on allergic rhinitis

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## Abstract

**Objective:** The purpose of this case control study is to establish the influence of iris color and retina pigment epithelium melanin on allergic rhinitis.

**Methods:** Ninety-nine subjects diagnosed prospectively as allergic rhinitis and 85 control subjects were included in the study. Color of iris was recorded after ophthalmic examination. Electro-oculographic measurement was done after pupil dilatation and Arden ratios were recorded.

**Results:** Mean age was 29.44±9.8 years in subject with allergic rhinitis and 32.67±12.9 years in control subjects (p>0.05). Measured mean Arden ratio was 158.22±29.4 in subjects with allergic rhinitis and 179.34±29.3 in normal subjects (p<0.05). In control group, Arden ratio was significantly higher in eyes with brown iris (p<0.05). In subjects with allergic rhinitis, Arden ratio was significantly lower in brown eyes (p<0.05).

**Conclusion:** An association between allergic rhinitis and melanin content of iris and retina pigment epithelium was found. It can be speculated that pigment-producing system may play a role in the pathogenesis of the allergic rhinitis.

**Keywords:** Allergic rhinitis, iris color, retina pigment epithelium, Arden ratio, melanin.

## Özet: İris rengi ve retina pigment epitel melanininin alerjik rinite olan etkisi

**Amaç:** Bu olgu kontrol çalışmasının amacı, iris rengi ve retina pigment epitel melanininin alerjik rinite olan etkisini saptamaktır.

**Yöntem:** Çalışmaya 85 kontrol denek ve prospektif olarak alerjik rinit tanısı konan 99 hasta alındı. Göz muayenesinden sonra iris rengi kaydedildi. Pupil dilatasyonundan sonra elektrookülografik ölçüm yapıldı ve Arden oranları kaydedildi.

**Bulgular:** Yaş ortalaması alerjik rinitli hastalarda 29.44±9.8 yıl, kontrol deneklerde 32.67±12.9 yıl idi (p>0.05). Ölçülen Arden oranı ortalaması alerjik rinitli hastalarda 158.22±29.4, kontrol deneklerde 179.34±29.3 idi (p<0.05). Kontrol grubunda Arden oranı kahverengi irisi olan gözlerde anlamlı derecede daha yüksekti (p<0.05). Alerjik rinitli hastalarda Arden oranı kahverengi irisi olan gözlerde anlamlı derecede daha düşüktü (p<0.05).

**Sonuç:** Alerjik rinit ile iris ve retina pigment epitelinin melanin içeriği arasında bir ilişki bulunmuştur. Pigment üretici sistemin alerjik rinit patogenezinde rol oynayabileceği öne sürülebilir.

**Anahtar sözcükler:** Alerjik rinit, iris rengi, retina pigment epiteli, Arden oranı, melanin.

Allergic rhinitis is an increasingly common disorder which manifests itself with symptoms of itchy nose, rhinorrhea, sneezing and nasal congestion as a result of exposure of sensitized individuals to certain antigens. The release of vasoactive mediators such as histamine, leukotrienes, prostaglandins, cytokines and tryptase follows after allergens

bind specific IgE on the surfaces of basophils and mast cells and they show their effects in nasal vasculature by their receptors to result in either vasoconstriction and vasodilatation. Alterations in vascular innervation can be one of the reasons in regards of the continuity of allergic rhinitis.<sup>[1]</sup> Normally, a constant release of noradrenaline is thought to

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keep the sinusoidal veins partially contracted due to the fact that the vasoconstrictor effects of stimulation of  $\alpha$ -adrenoreceptors is more evident than vasodilatation after the stimulation of  $\beta$ 2-receptors.<sup>[2]</sup> So, there is a continuous balance between pro-constrictory and pro-dilatory vasoactive forces, which establishes the basal sinusoidal tone. It was suggested that in allergic rhinitis, H3 receptors assist nasal blockage by inhibition of a basal sympathetic vasoconstricting tone.<sup>[3]</sup> Melanin is the basic chromophore of the human iris and it is regarded to be the most important reason which identifies the color of the irises. The melanocytes located in the iris of human and primate eyes take both cholinergic and adrenergic innervation and the adrenergic nervous stimulation has an effect on tyrosinase activity and iris color.<sup>[4]</sup> Retinal pigment epithelium (RPE) is an unilayer of pigment cells that lies between the neural retina and uveal tract and it is accountable for essential metabolic supplement to the whole retina and is in charge of phagocytosis of the photoreceptor outer segment disks. The electro-oculogram (EOG) is a commonly used test that measures the effect of dark and light to the standing potential between RPE and photoreceptor complex providing to evaluate the integrity of the RPE-photoreceptor complex. Arden ratio refers the calculation between the lowest dark adapted point (dark trough) and highest light point (light peak). Reduced Arden ratios of the EOG indicate dysfunction of the photoreceptor retinal pigment epithelium complex.<sup>[5]</sup>

Melanocytes can also play roles as regulators of the immune responses of the skin following UV exposure via providing some cytokines, including TNF- $\alpha$ , IL-1, IL-2 and IL-3, which are mediators also in allergic rhinitis.<sup>[6]</sup> Synnerstad et al.<sup>[7]</sup> found that the children who were reported to have any of the allergic diseases, 79% of them were blonde and 77% were blue eyed and they also found that the children who were reported to have active atopic dermatitis have marked lower nevi than children without atopy. Allergic rhinitis have many common physiopathologic properties with atopic dermatitis, a skin disorder that is successfully cured by phototherapy. Recently, phototherapy is also evaluated as an influential therapy in the management of allergic rhinitis.<sup>[8,9]</sup> These findings suggest that there may be a relationship between allergic disorders and pigmentation. In the present study, it is aimed to determine whether the iris color and RPE influences allergic rhinitis.

## Materials and Methods

This study was planned as a prospective study and implemented in the departments of otolaryngology and ophthalmology. The study was endorsed by the Institutional Ethics

Committee and written informed consent was obtained from each of the patients.

Allergic rhinitis was diagnosed by history, physical examination, prick test (Stallergenes S.A., Cedex, France) and serum IgE results. Allergic rhinitis was diagnosed with the presence of the symptoms such as itchy nose, rhinorrhea, sneezing and nasal congestion. Control group consisted of normal subjects without any systemic or ocular disease.

In all patients, visual acuity was recorded using Snellen chart, and biomicroscopic anterior segment examination was done while the iris color was subjectively defined by two doctors, one was from the ophthalmology department and the other was from the otolaryngology department. Fundus examination was done by a 90 diopters lens. Any patient who had abnormal visual acuity and funduscopy findings was excluded. The EOG test was performed to all subjects according to the ISCEV (International Society for Clinical Electrophysiology of Vision) protocol. After pupil dilatation with topical tropicamide 1% (Tropamid fort, Bilim, Istanbul, Turkey) and phenylephrine hydrochloride 2.5% (Mydrin, Alcon, Fort Worth, TX, USA), EOG was performed (MonElec 2, Metrovision, Perenchies France). The patient head was rested on a chin rest at 33 cm. Four cupula electrodes were placed to the lateral and medial canthus of the right and the left eye. After a dark phase of 12 minutes, light phase lasting 12 minutes was performed. So, 8 saccades under dark conditions and 8 saccades under light conditions were completed. Saccade amplitude was 50 degrees and light phase was performed at 100 cd/m<sup>2</sup>. After the test was completed, the light peak/dark trough ratio (Arden ratio) was recorded. Arden ratios were compared for two groups and evaluated according to the iris colors.

Statistical analysis was performed using the Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparison of two groups for iris color was computed by Mann-Whitney U test. Mean Arden ratios between two groups were evaluated by independent samples t-test. Iris color distribution between the groups was evaluated by chi-square test. Within each group, change in mean Arden ratio according to the iris color was calculated by Kruskal-Wallis test. At all times, p values <0.05 were regarded as statistically significant.

## Results

Ninety-nine patients with allergic rhinitis were included in the study. The control group consisted of 85 normal subjects. Mean age was 29.44 $\pm$ 9.8 years in the study group, whereas it was 32.67 $\pm$ 12.9 years in the control group (p>0.05). In the study group, 68 (62.4%) patients were

female and 31 (41.3%) were male, whereas in the control group, 41 (37.6%) subjects were female and 44 (58.7%) subjects were male.

In the study group, color of iris was not recorded in 6 subjects. For the recorded patients with allergic rhinitis, 39 (41.9%) subjects had brown iris, 38 (40.9%) subjects had hazel iris and 16 (17.2%) subjects had blue iris. In the control group, 57 (67.1%) subjects had brown iris, 16 (18.8%) subjects had hazel iris and 12 (14.1%) subjects had blue iris ( $p < 0.05$ ) (Fig. 1). Numbers of hazel iris and blue-colored iris were significantly higher in the study group compared to brown iris ( $p < 0.05$ ). Brown iris was found to be lower in the patients with allergic rhinitis.

Mean Arden ratio was found to be significantly lower in the study group. It was  $158.22 \pm 29.4$  (107–227) in the study group and  $179.34 \pm 29.3$  (143–243) in control group ( $p < 0.05$ ). Mean Arden ratio in groups according to iris color was given in Table 1. Arden ratio was found to be significantly lower in brown iris in the patients with allergic rhinitis as compared to study group, while no differences were present for the hazel and blue irises between the two groups. In the study group, Arden ratio was lower in subjects with brown iris compared to hazel and blue iris ( $p < 0.05$  and  $p < 0.05$  respectively), whereas there was no significant difference between hazel and blue irises ( $p > 0.05$ ). In the control group, Arden ratio was significantly lower in subjects with hazel or blue iris compared to brown iris ( $p < 0.05$  and  $p < 0.05$  respectively), whereas there was no significant difference between hazel and blue irises ( $p > 0.05$ ).

### Discussion

In this study, we attempted to demonstrate whether there was a relationship between allergic rhinitis and melanin content of iris and RPE. To the extent of our knowledge, this is the first study in English literature that showed an association between allergic rhinitis and melanin content of iris and RPE.

The present study shows that the ratio of brown iris in the patients with allergic rhinitis is significantly lower, whereas the percentages of hazel and blue irises are found to be significantly higher. This result shows that the light-colored eye has higher risk for the development of allergic rhinitis so that decreased melanin pigment content in the iris is related with increased incidence of allergic rhinitis.

The wall of the human eye is composed of three parts, the retina, the uveal tract, and the opaque white sclera and transparent cornea. The uveal tract further consists of three

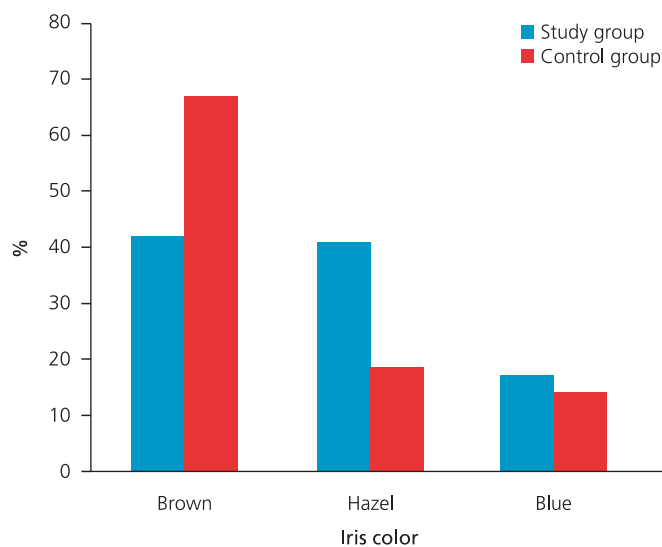


Fig. 1. Distribution of the iris colors among the patient and the control groups.

layers, from anterior to posterior—the iris, the ciliary body and the choroid. Pigmented cells are divided into two-different types—the pigment cells and the uveal melanocytes localized in the uveal tract. The uveal melanocytes also consist of iridal, ciliary and choroidal melanocytes. The melanocytes in human iris produce both the reddish-yellow pheomelanin and brown-black eumelanin. The melanin content in the iridial melanocytes is the most important distinctive mark of the eye color. Despite the number of melanocytes in brown, hazel and blue irises have been reported to be very comparable, the quantity of uveal melanin in eyes with dark-colored irises (dark brown and brown) is much more than that in light-colored eyes (yellow-brown, green, hazel and blue).<sup>[10]</sup> Darker irises have larger granule density and greater melanin granules. Lower tyrosinase activity and melanin content were reported in

Table 1. Mean Arden ratio in groups according to iris color.

Iris color	Allergic rhinitis (n=99)	Control group (n=85)	p1
All	158.22±29.4	179.34±29.3	<0.05
Brown	148.36±21.8	187.86±31.1	<0.05
Hazel	167.00±37.0	163.25±17.2	>0.05
Blue	162.50±19.5	160.33±9.9	>0.05
p2	<0.05	<0.05	

p1: Independent samples t-test; p2: Kruskal-Wallis test.

uveal melanocytes cultured from light-colored irises.<sup>[11]</sup> The melanosomes are the organelles that contain melanin in the pigment cells, and are involved with lysosomes. While the melanosomes are few and often not fully developed in the iridial melanocytes of blue-eyed individuals, they are a lot and of grade III–IV in brown-eyed individuals.<sup>[12]</sup>

The iris which is certain in Caucasian infants begins with a clear blue color and then becomes brown in the more melanized persons or remains blue in the less melanized ones.<sup>[13]</sup> As far as the eye is exposed to sunlight, melanin pigment is started to be produced by the iris and color of the eye progressively changes towards the color of the adult stage and pigmentation is completed by age 3. At post early childhood and during adulthood, the eye color may change in 10–15% of Caucasians. As the eye color itself, the tendency to change the eye color may be an inherited trait. Depigmentation and or atrophy of the iris can be seen in various non-inflammatory and inflammatory status including trauma, Horner's syndrome, Waardenburg syndrome, acute angle closure glaucoma, viral iridocyclitis and Fuchs' uveitis syndrome.<sup>[14]</sup> It is very interesting that the generally accepted treatment of glaucoma relied on  $\beta$ -adrenergic blockers, selective  $\alpha$ -adrenergic agonists (e.g. clonidine) and prostaglandin analogues. Latanoprost, a prostaglandin F2 $\alpha$  derivative that has been used successfully for the glaucoma treatment has an interesting side effect; an iridial pigmentation increase in 5–15% of the patients, even the highest number of side effects has occurred in patients with heterochromatic (e.g. green/brown or blue/brown) or hazel eye color.<sup>[15]</sup> Besides the iridial pigmentation side effect, in some patients, latanoprost have been shown to result in longer and darker eye lashes.<sup>[16]</sup> Similarly, physical examination of the head in allergic rhinitis may reveal some characteristic findings such as dark discoloration under the eyes, or "allergic shiners" which is attributed to venous engorgement.<sup>[17]</sup> In individuals with allergic rhinitis, concentrations of prostaglandins PGE2 and PGD2 are found to be increased following allergen challenge in lavage fluid.<sup>[1]</sup> Also, in addition to epinephrine, three beta-adrenergic agonists; isoproterenol, salbutamol and metaproterenol have recently been demonstrated to lead to evident proliferation of iridial melanocytes in vitro, raising the number of the cells around 300%.<sup>[18]</sup> In Horner's syndrome which occurs as a result of a lesion anywhere along the oculosympathetic pathway, McCartney et al.<sup>[19]</sup> found that there was marked lack of sympathetic axons and the number of stromal melanocytes was reduced in the affected eye. Melanocytes are in close relationship to adrenergic innervation and

adrenergic agonist agents stimulate melanogenesis and growth in uveal melanocytes. Nasal obstruction and rhinorrhoea were reported symptoms associated with Horner's syndrome and cervical sympathetic paralysis.<sup>[20]</sup> Nasal congestion was seen following cervical sympathectomy and antihypertension drugs, whereas basal activation of  $\alpha$ 1-adrenoceptors prevented "automatic" nasal blockage.<sup>[3]</sup>

Mean Arden ratio was found to be significantly lower in the patients diagnosed with allergic rhinitis as compared to the control group. Meanwhile, Arden ratio was decreased more in the patients with brown iris compared to hazel and blue iris in the study group. This present result indicates that melanin content decreased in RPE of the patients with allergic rhinitis. The EOG is believed to show RPE and rod/cone interactions of the human eye, hence it was regarded to be an effective non-invasive diagnostic instrument.<sup>[5]</sup> The lower EOG dark trough values have been determined in albinism, which is characterized with congenital decline or total absence of pigment in eyes, skin and hair.<sup>[21]</sup> On the other hand; in neurofibromatosis type 1 disease which includes hyperpigmented skin lesions, cutaneous and plexiform neurofibromas, Lisch nodules and optic gliomas, the Arden ratios of the EOG test were considerably higher.<sup>[22]</sup>

Retina pigment epithelium is a monolayer of cells that are linked by tight junctions near the apical surface. These junctions separate the basal and apical membranes of the pigment epithelium, which have different ionic permeability characteristics that lead to the generation of a voltage across the cell. This voltage, called the standing potential, is positive at the cornea and measures 6–10 mV. The change in this voltage throughout the human eye stimulated by the alteration of illumination constitutes the base of the clinical EOG. The EOG needs RPE membrane integrity, however it is not a pure test of RPE function, as photoreception of the retina is necessary and as the light response is not known to be related with any specific retinal or RPE function (including vision, visual pigment regeneration and RPE water transport).<sup>[23]</sup> In EOG, a light rise is due to the release of a substance which prompts an increase in the intracellular calcium concentration within the RPE. Increase of intracellular calcium results in basal membrane depolarization by opening a basolateral ionic Cl<sup>-</sup> channel. Most of the fluid regulation in the RPE is managed by calcium-gated Cl<sup>-</sup> channels and the aquaporins, expressed also by cultured normal human nasal epithelial cells.<sup>[24]</sup> The EOG changes in response to mannitol, acetazolamide, alcohol, hypoxia, and hyperoxia have all been investigated as potentially available non-photic stim-

uli which directly influence the RPE. These results demonstrate the metabolic influences on the transepithelial potential of the RPE.<sup>[25]</sup> Adrenergic and muscarinic receptors have been demonstrated at the apical membrane of the RPE and a mechanism on the RPE apical surface is obviously a “receptor” for epinephrine, even at micromolar concentration.<sup>[26]</sup> Melanin in RPE is involved in many important functions including light protection, protection from oxidative stress, detoxification of peroxides. While the light-colored eye is risky for the development of uveal melanoma, the lower incidence of age-related macular degeneration in dark-colored eyes can be involved with lower light intensity that can reach to the retina.

Ultraviolet irradiation (UVR) is a major stimulus of facultative pigmentation. Melanocyte, a kind of specialized dendritic cell can secrete a large number of signal molecules such as cytokines (nitric oxide, TNF- $\alpha$ , IL-1, IL-3 and IL-6), serotonin, eicosanoids, and catecholamines, in response to UVR. Phototherapy can effectively attenuate the effector stage of allergic rhinitis at different checkpoints by inhibiting secretion and synthesis of pro-inflammatory mediators, by inducing apoptosis of the immune cells (T and B cells, eosinophils and dendritic cells) and by decreasing the antigen presenting capacity of the dendritic cells.<sup>[27]</sup>

Synnerstad et al.<sup>[7]</sup> found that the children with atopic dermatitis have significantly fewer nevi than children without atopy. They reported that why children with atopic dermatitis have few nevi is not known, whereas the reason might be due to altered immune responses, genetic factors or effect of various treatments including UVR and topical steroids. They postulated that the pro-inflammatory cytokines in the atopic skin may influence melanocyte growth and/or progression to nevi negatively. Awaya et al. found that people exhibiting conspicuous nevi are resistant to pollinosis and suggested that people who have weak nevi-producing systems are more susceptible to pollinosis and that systems inducing the occurrence of pollinosis and those producing nevi are competing with each other, so that nevi may delay or inhibit the occurrence of pollinosis.<sup>[28]</sup>

It could be thought that there was no relationship between nasal mucosa and the human eye. Everett<sup>[29]</sup> reported that sneezing can be produced by exposure of the eyes to bright light. Moreover, Ozsutcu et al.<sup>[30]</sup> reported that the pupil size in response to photic stimuli in children with allergic rhinitis was smaller than that of the control group and may indicate parasympathetic hyperactivity and sympathetic hypoactivity. Several hypotheses such as common adrenergic control or ion channels could be devel-

oped to explain the relationship between allergic rhinitis and melanin content of iris and RPE, whereas further studies are needed to confirm.

Our study being relatively small size of our subjects, lack of definite criteria for selection of patients, lack of demographic data regarding especially lifestyle, geographic and climatic reasons, and finally being a single-center study were the limitations of this study. However, we hope that this study will pioneer not only further studies about the relationship between the iris color and the allergic rhinitis, but also to better understanding of pathophysiologic mechanisms of allergic rhinitis.

As Tsatmali et al.<sup>[31]</sup> proposed that the pigment system plays a modulating, down-regulating response to all forms of cutaneous inflammation whether induced by sunlight, infections, or injuries; we can speculate that pigment-producing system may have a role in the pathophysiology of allergic rhinitis.

**Conflict of Interest:** No conflicts declared.

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# Long-term outcomes of functional surgery for attic cholesteatoma

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## Abstract

**Objective:** To evaluate the long-term findings obtained using microscopic approaches to attic cholesteatoma and with respect to the reconstruction materials used in ossiculoplasty.

**Methods:** The results of these procedures were evaluated in 30 of the patients who subsequently returned for follow-up. One of the surgical techniques among atticotomy + tympanoplasty, intact canal wall tympanoplasty (ICWT) and canal wall-down tympanomastoidectomy (CWDT) was performed. The responses to procedures based on postoperative complaints, otoscopy and audiometry results were evaluated and compared with those pre-treatment.

**Results:** A comparison of the preoperative and postoperative air-bone differences in 26 (85%) patients showed a hearing gain of 5–35 dB. The largest gain was achieved with ICWT type II surgery. Evaluation of the tympanic membrane by microscopic otoscopy showed various degrees of retraction in 30% of the patients in the open group and approximately 20% of those in the closed group. After a six-year long-term follow-up, 55% of the patients in the open group and 45% of those in the closed group had normal findings.

**Conclusion:** An adequate exposure allowing full removal of an attic cholesteatoma may require an open technique. Compared to closed techniques, this also allows hearing preservation and ossicular reconstruction. Good results in the reconstruction of the ossicles can be achieved using recently developed biomaterials, assuming that the stapes and manubrium mallei are in good condition.

**Keywords:** Otitis media, ossiculoplasty, attic, cholesteatom.

## Özet: Attik kolesteatom fonksiyonel cerrahisinin uzun dönem sonuçları

**Amaç:** Çalışmanın amacı, attik kolesteatom cerrahisi ve ossiküloplastisinde kullanılan rekonstrüksiyon malzemeleri ile ilgili cerrahi tekniklerden elde edilen uzun dönem sonuçların değerlendirilmesidir.

**Yöntem:** Uygulanan prosedürlerin sonuçları, uzun dönem takibi için ulaşılabilen 30 hastada değerlendirildi. Hastalara attikotomi + timpanoplasti, intakt kanal timpanoplasti (ICWT) ve açık kanal timpanomastoidektomi (CWDT) prosedürlerinden biri uygulandı. Ameliyat sonrası şikayetler, otoskopi, odyometri sonuçlarına göre prosedürler değerlendirilip tedavi öncesi ile karşılaştırıldı.

**Bulgular:** Yirmi altı (%85) hastada preoperatif ve postoperatif hava-kemik yolu farkları karşılaştırıldığında 5–35 dB işitme kazancı görüldü. En büyük kazanç ICWT tip II cerrahi ile elde edildi. Mikroskopik kulak zarı değerlendirilmesinde, açık teknik grubundaki hastaların %30 ve kapalı teknik grubunda olanların yaklaşık %20'sinde değişik derecelerde retraksiyon izlendi. Altı yıllık takipte açık gruptaki hastaların %55 ve kapalı grupta olanların %45'inde normal bulgular mevcuttu.

**Sonuç:** Attik kolesteatomun tamamen çıkarılması açık teknikler gerektirebilir. Kapalı tekniklerle karşılaştırıldığında, açık teknikte de işitme korunması ve kemikçik rekonstrüksiyonu sağlanabilir. Stapes ve manubrium malleinin iyi durumda olduğu durumlarda yeni geliştirilen biyomalzemeler kullanılarak çok iyi sonuçlar elde edilebilir.

**Anahtar sözcükler:** Otitis media, ossiküloplastisi, attik, kolesteatom.

Since the first description of atticotomy in 1889, by Küster, numerous successful surgeries for attic cholesteatoma have been conducted.<sup>[1]</sup> New and more

functional approaches to the eradication of cholesteatoma have arisen from a better understanding of the possible differences in the biological effects of cholesteatoma in

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relation to its location, and from novel surgical techniques and reconstruction materials.<sup>[2,3]</sup> In this paper, we present the results of a systematic retrospective review that may help to evaluate the findings obtained using microscopic approaches to attic cholesteatoma and with respect to the reconstruction materials used in ossiculoplasty.

### Materials and Methods

Between January 1992 and December 1993, 64 patients were operated for attic cholesteatoma at our Ear, Nose and Throat (ENT) Department. The results of these procedures for 30 of the patients who subsequently returned for follow-up in 1998 were evaluated. Data on the surgical technique, postoperative complaints, otoscopy results, whether revision surgery was performed, pure tone audiometry results at 500–1000–2000 Hz, and postoperative long-term air and bone conduction averages were considered. The age range of 14 female (46.6%) and 16 male (57.4%) patients was 8–57 years, with an average age of 25.7 years. Data on the age are presented in Fig. 1. After their admission to the clinic, all patients underwent audiometric testing and evaluation of their complaints. Following a routine ENT examination and microscopic otoscopy in our laboratory, pure tone audiometry was conducted. Six of the patients underwent otoendoscopy using endoscopes with diameters of 4 and 2.7 mm and an angle of 0°. Selected images from the monitor output were recorded.

The cholesteatomas were located at or around the attic in all patients: atticotomy + type I tympanoplasty was performed in 10% of cases, atticotomy + type II tympanoplasty in 6.6%, atticotomy + type III tympanoplasty in 6.6%, intact canal wall tympanoplasty (ICWT) type I in 6.6%, ICWT type II in 3.3%, ICWT type III in 6.6%, canal wall-down tympanomastoidectomy (CWDT) type I in 10%, CWDT type II in 36.3%, and CWDT type III in 13.3%. Data on the procedures are presented in Fig. 2.

Ossiculoplasty was performed in 22 (72.6%) patients, with autologous ossicular material used in 11 (5%) of these patients, artificial ossicular material in 10 (45.4%) patients, and homologous ossicular material in one (4.6%) patient. As tympanic membrane reconstruction material, autologous temporalis muscle fascia was used in 29 patients (95.7%). Data on the ossiculoplasty materials used are presented in Fig. 3.

During postoperative follow-up, the otoscopy findings, postoperative complaints, need for revision surgery, postoperative vs. preoperative audiometry, and audiometric test results were evaluated and compared between the patients.

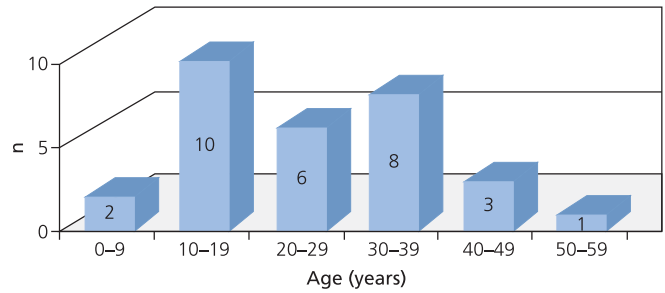


Fig. 1. Data on the age.

### Results

Data on the surgical technique, postoperative complaints, otoscopy results, whether revision surgery was performed, pure tone audiometry results at 500–1000–2000 Hz, and postoperative long-term air and bone conduction averages were considered. A comparison of the preoperative and postoperative air-bone differences in 26 (85%) patients showed a hearing gain of 5–35 dB. In three patients, no change was detected and in one patient a 10 dB hearing loss was measured. The average gains depending on the operation type are presented in Fig. 4. The largest gain was achieved with ICWT type II surgery.

The results of 12 patients treated using a closed technique and the 18 patients treated using an open technique

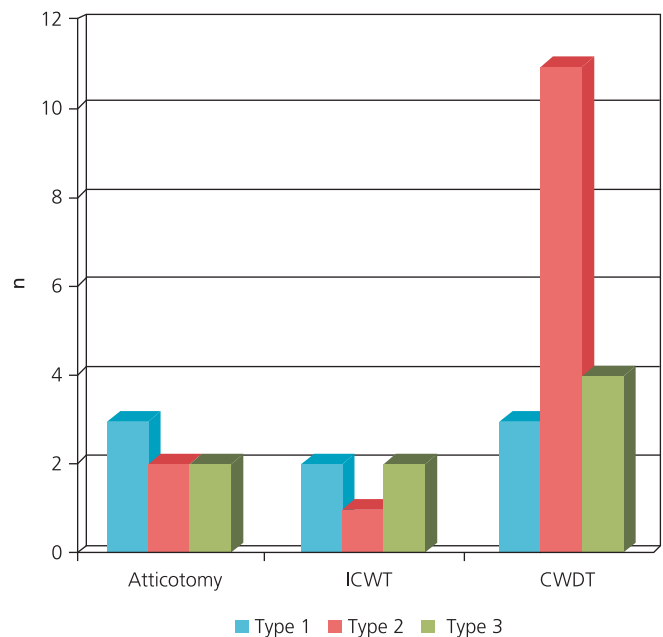


Fig. 2. Data on the procedures.

were analyzed statistically using a Mann-Whitney U test. The difference between the two techniques was not significant ( $p=0.249$ ). Among the 22 patients who underwent ossiculoplasty, the best results in terms of hearing gain were obtained when an incus prosthesis or a partial ossicular replacement prosthesis (PORP) was used.

Evaluation of the tympanic membrane by microscopic otoscopy showed various degrees of retraction in 30% of the patients in the open group and approximately 20% of those in the closed group. The perforation rates were 5.5% (1 patient) and 12% (1 patient), respectively. In addition, tympanosclerosis was detected in 24% of the closed cases (2 patients) and 11% of the open cases (2 patients). After a six-year long-term follow-up, 55% of the patients in the open group and 45% of those in the closed group had normal findings. One patient, operated on with the closed technique, had a recurrence several years postoperatively. Revision surgery was performed using the open technique.

### Discussion

The extend pattern of the cholesteatoma is defined by the site of origination. The most common sites are the pars flaccida and the postero-superior of the pars tensa. Retraction pockets especially can cause attic cholesteatoma. Intense mucosal disease and eustachian tube dysfunction may contribute to unfortunate outcomes. The diagnosis of attic cholesteatoma is substantially clinical and treatment is surgical. The fundamental purpose of surgery is to supply a disease-free and functionally better ear.<sup>[1-4]</sup>

Since the first description of atticotomy in 1889, numerous successful surgeries for attic cholesteatoma have been conducted. In recent times, sophisticated surgical technology and autologous ossicular materials have facilitated the functional surgery for attic cholesteatoma.<sup>[1,2]</sup> In this study, seven patients with cholesteatoma who underwent tympanoplasty using different techniques combined with atticotomy had a hearing gain of approximately 12 dB. Buckingham also advocated standard tympanomastoid operations for cholesteatomas that spread to the eardrum and mastoid, or in which ossicular injury occurred, or in early-stage epitympanic cholesteatoma lateral to the ossicles.<sup>[5]</sup> In these patients, atticotomy can maintain a normal or near-normal hearing level. If there is an intact head of malleus and incus body, attic reconstruction is possible and atticotomy could lead to improved hearing. However, postoperative retraction seen in some of patients, a problem that will need to be solved in the future.<sup>[6,7]</sup> In our surgical patients, we pre-

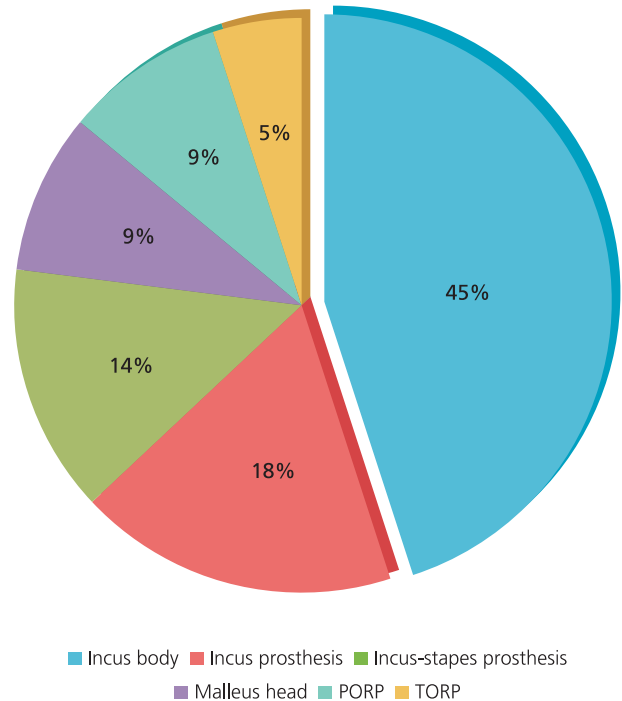


Fig. 3. Data on the used ossiculoplasty materials.

fer to remove the anterior attic bony plate or cog via a transmastoidal approach. In their large series of patients with long-term follow-up in whom anterior tympanotomy operations were not possible. Morimuts et al. found that this strategy reduced the recurrence rate from 17% to 4%.<sup>[8]</sup>

The symptoms in attic cholesteatoma are often relatively mild, as hearing loss generally occurs only in the late stage. Therefore, many of these patients will not be referred

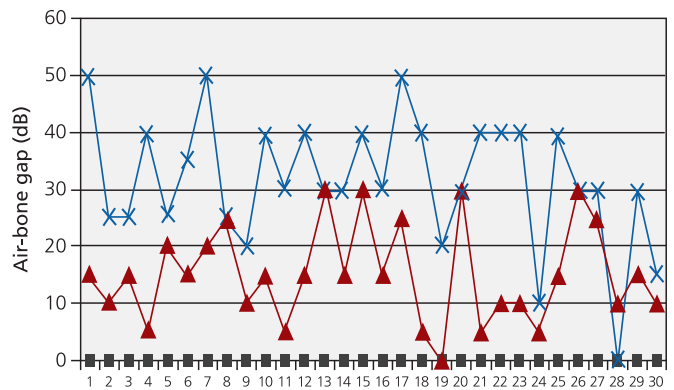


Fig. 4. The average gains are shown, in which the blue line (x) represents preoperative and red line (▲) represents postoperative air-bone gap (dB).

for timely surgery and those with normal hearing or only slight hearing loss will not seek prompt medical attention.<sup>[1,9]</sup> Among the patients who underwent CWDT for attic cholesteatoma, the mastoid cavity was closed in 10%, whereas 65% had a small cavity and 25% had a large cavity. In approximately 85%, the cavity remained dry; in more than half of these cases the cavity was self-cleaning whereas in 15% cavity problems developed. In our study, 12% of the patients in the closed group and 5% of those in the open group had perforation. Varying degrees of retraction were detected in 30% and 20%, respectively. The four patients in whom tympanosclerosis developed were monitored; none of them had an effusion of the middle ear. CWDT is an adequate treatment for attic cholesteatoma. The functional outcomes are satisfying. A tympanoplasty can be performed simultaneously. Therefore, in the majority of patients, only a single operation is required. However, CWDT creates an open cavity and modifies the physioanatomy of the middle ear and mastoid. This may cause ear discharge, difficulty in fitting a hearing aid, and potentially a lifetime of outpatient procedures. The ICWT procedure eliminates the need to destroy the middle ear and mastoid, but it is associated with a higher rate of residual cholesteatoma.<sup>[6,10,11]</sup> Open procedures are necessary when the disease has destroyed the posterior canal wall or in cases associated with intracranial complications.<sup>[12]</sup>

The good hearing outcome is an air-bone gap between 0 and 20 dB for the three frequencies 0.5, 1 and 2 kHz. Tos and Lau found that 36% of patients with a CWDT had an air bone gap  $\leq 20$ , and 50% of patients with an ICWT had an air bone gap  $\leq 20$  dB.<sup>[13,14]</sup> Our long-term hearing outcomes are comparable to other authors' results.<sup>[14-19]</sup> Ossiculoplasty with PORPs had slightly better postoperative hearing than with TORPs. An intact posterior canal wall and a stapes suprastructure are essential to superior hearing outcome.<sup>[20]</sup>

## Conclusion

In conclusion, there are different surgical procedures for eliminating attic cholesteatoma. Although this study was carried out in 1999, since then surgical techniques that are commonly used for attic cholesteatoma have not changed. An adequate exposure allowing full removal of a cholesteatoma may require an open technique. Compared to closed techniques, this allows hearing preservation and ossicular reconstruction. A successful external ear canal plasty can then be easily performed to obtain a smooth, widened, and open cavity. Good results in the reconstruction of the ossicles can be achieved using recently devel-

oped biomaterials, assuming that the stapes and manubrium mallei are in good condition. However, in patients in whom the upper aspect of the stapes is absent, satisfactory hearing results are still possible by combining biomaterials with autograft cartilage. Middle ear implants represent in selected patients a new remedy to rehabilitate the persistent hearing losses.<sup>[21]</sup> The selection of surgical procedure should be individually tailored based on the pre-operative otomicroscopy, hearing and imaging findings.

**Conflict of Interest:** No conflicts declared.

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# Clinical and microbiological evaluation of the culture results of the patients with chronic dacryocystitis at a tertiary care hospital

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## Abstract

**Objective:** In this study, we aimed to evaluate the isolated strains from the patients with chronic dacryocystitis and the relationship between different anatomical areas and their antibiotic susceptibilities.

**Methods:** Fifty patients diagnosed with chronic dacryocystitis were included. Fifty patients underwent endoscopic endonasal dacryocystorhinostomy from March 2013 to April 2014. Swab samples were obtained from conjunctiva and inferior nasal meatus before surgery, obtained from lacrimal sac during surgery. Identification and antibiotic susceptibility of the isolated strains were performed by automated Vitek version 2.0 systems (BioMérieux Inc., Marcy-l'Étoile, France).

**Results:** A total of 39 (78%) female and 11 (22%) male patients were operated and 150 swab samples were evaluated. Bacterial growth was detected in 136 (90.6%) culture samples. A single (n=125; 91.9%) or two different (n=11; 9.1%) microorganisms were grown on culture media. The distribution of gram-positive strains (n=91) and gram-negative strains (n=56) were 61.90% and (38.10%), respectively. The most frequently isolated gram-positive isolate was *Staphylococcus*. Gram-negative isolates were susceptible to third-generation cephalosporins, cefepime and carbapenems while gram-positive isolates were susceptible to vancomycin, teicoplanin and linezolid.

**Conclusion:** For methicillin-sensitive coagulase-negative *Staphylococci* and methicillin-resistance coagulase-negative *Staphylococci*, bacterial growth demonstrated similarities among three different compartments (conjunctiva, lacrimal sac and inferior meatus). In other words, growth of these microorganisms in one location points to their proliferation in the other location or vice versa. This data can be used to guide antimicrobial therapy for these cases; but further studies are required.

**Keywords:** Chronic dacryocystitis, conjunctival flora, lacrimal sac, culture.

## Özet: Bir üçüncü basamak hastanesindeki kronik dakriyosistit hastalarının kültür sonuçlarının klinik ve mikrobiyolojik değerlendirilmesi

**Amaç:** Bu çalışmada, kronik dakriyosistitli hastalardan izole edilen örnekler yardımıyla farklı anatomik bölgeler ile bunların antibiyotik duyarlılığı arasındaki ilişkinin incelenmesi amaçlanmıştır.

**Yöntem:** Kronik dakriyosistit tanısı konmuş ve Mart 2013 ile Mayıs 2014 arasında endoskopik endonazal dakriyosistorinostomi ameliyatı geçiren 50 hasta çalışma kapsamına alındı. Swab örnekleri konjunktiva ve alt nazal meatustan ameliyat öncesi, lakrimal kese örnekleri ise ameliyat sırasında alındı. İzole edilmiş örneklerin tanımlanmasında ve antibiyotik duyarlılığının belirlenmesinde Vitek versiyon 2.0 sistemleri kullanıldı (BioMérieux Inc., Marcy-l'Étoile, Fransa).

**Bulgular:** Otuz dokuz kadın (%78), 11'i erkek (%22) toplam 150 hasta ameliyat edildi ve kendilerinden swab örnekleri alındı. Kültür örneklerinin 136'sında (%90.6) bakteri gelişimi saptanmıştır. Kültür ortamında tek (n=125; %91.9) veya iki farklı (n=11; %9.1) mikroorganizma ekimi yapıldı. Gram-pozitif ve gram-negatif örneklerin dağılımı sırasıyla %61.9 (n=91) ve %38.1 (n=56) oldu. En çok rastlanan gram-pozitif örnek *Staphylococcus* idi. Gram-negatif izolatlar 3. nesil sefalosporinlere, sefepime ve karbapenemlere duyarlılık gösterirken gram-pozitif izolatlar vankomisin, teikoplana ve linezolide duyarlılık gösterdi.

**Sonuç:** Metisilin duyarlı koagülaz-negatif *Staphylococci* ve metisilin dirençli koagülaz-negatif *Staphylococci* için bakteri büyümesi, konjunktiva, lakrimal kese ve alt meatus olmak üzere üç bölgede benzerlik göstermiştir. Başka bir deyişle bu mikro-organizmaların bir lokasyonda büyümesi başka bir lokasyonda da hızla büyüyebileceklerini göstermektedir.

**Anahtar sözcükler:** Kronik dakriyosistit, konjunktiva florası, lakrimal kese, kültür.

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Chronic dacryocystitis is an inflammatory process of the lacrimal sac associated with total or partial occlusion of the lacrimal duct. Obstruction of the lacrimal system can emerge secondary to idiopathic, traumatic, mechanical obstruction and/or infection. Microorganisms colonized within the occluded lacrimal system can presumably cause inflammation.<sup>[1-3]</sup> In studies where bacterial colonization in conjunctiva, lacrimal duct and sac in patients with chronic dacryocystitis were analyzed, various outcomes have been encountered within years. Mixed bacteria, *Staphylococci spp.* or *Streptococci spp.* are frequently isolated bacteria.<sup>[1-4]</sup> In the pathology of chronic dacryocystitis, surgical fistula constructed to establish a communication between occluded lacrimal duct and nasal passage through external or endonasal approach is called dacryocystorhinostomy. This procedure is the gold standard in the surgery of chronic dacryocystitis. Dacryocystostomy enables patency of the occluded lacrimal duct and lacrimal fluid flow is maintained thanks to mechanical communication between lacrimal sac and nasal passage. This mechanical communication ensures lacrimal drainage and eradication of the causative colonized bacteria, which gained pathogenicity. However, this assumption has not been proved conclusively.<sup>[5-7]</sup> In this study, we aimed to evaluate the isolated strains from the patients with chronic dacryocystitis and the relationship between different anatomical areas and their antibiotic susceptibilities.

## Materials and Methods

### Study design

Tepecik Training and Research Hospital is a tertiary care center with 1200 beds. This prospective study was approved by the Ethics Committee of this hospital (2013/02). Patients were monitored and surveyed in accordance with the Helsinki Declaration of 1975, as revised in 1983. All patients provided written informed consent before being enrolled in the study. Volunteer participants between from March 2013 to April 2014 were included in this study. Signed enlightened consent forms, which explained details of the study. Our patients who consulted to our outpatient clinic with complaints of epiphora were jointly evaluated by ENT and Ophthalmology Departments. Lacrimal duct and lacrimal sac obstruction were examined preoperatively using lacrimal irrigation, Schirmer's test and dacryocystography. Patients with diagnosis of chronic dacryocystitis who experienced acute episodes or individuals who used antibiotics or underwent revision surgery within 3 weeks were excluded from the study.

### Outcome parameters

Swab samples were obtained from conjunctiva and inferior nasal meatus before surgery, obtained from lacrimal sac during surgery. By this method, we aimed to compare the culture results of conjunctiva (anatomic part before the occlusion), lacrimal sac (occlusion part), and inferior meatus (anatomic part after the occlusion).

### Surgical technique

Fifty patients with the diagnosis of chronic dacryocystitis underwent endoscopic endonasal dacryocystorhinostomy (EDCR) or intubation of silicon tubes under local anaesthesia in the operating room on a day care basis. All cases were operated under local anesthesia in our clinic's outpatient surgery unit. Patients were administered 1 mg/kg pethidine HCl IM, mg atropine IM, and 5 mg diazepam PO 45 min before the surgery. Local anesthesia was achieved by topical 2% pontocaine and injection of 2% lidocaine with 25/1000 epinephrine intranasally. 0.4% Oxybuprocaine was applied topically to the eye. 0° and 30° 4.0-mm endoscopic Hopkins telescopes manufactured by Storz company (Karl Storz GmbH & Co., Tuttlingen, Germany) were used with mounted camera.

### Bacterial isolates

In patients with the diagnosis of chronic dacryocystitis who underwent EDCR and silicone tube intubation, swab samples were retrieved preoperatively from conjunctiva and inferior nasal meatus and from lacrimal sac directly under sterile condition. Swab samples were obtained from conjunctiva and inferior nasal meatus before local application of eye drops and nasal tampons. Swab samples were especially taken from purulent drainage within lacrimal sac. Impact of environmental factors (nasal packing, regional bleeding, surgical instruments and endoscopes) and contamination of middle meatus were particularly avoided. Swab samples of conjunctiva, lacrimal sac and inferior nasal meatus were incubated on thioglycollate broth for 24–48 hours. The incubated broth medium has been cultivated on blood agar, chocolate agar and eosin-methylene blue agar. The identification and the antimicrobial susceptibility of the isolated strains were studied by automated Vitek version 2.0 systems (BioMeriux, Marcy-l'Étoile, France).

### Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Parametric tests were applied to data of normal distribution and non-parametric tests (Mc Nemar) were applied to data of questionably normal distribution.  $p < 0.05$  was considered as statistically significant.

## Results

Mean age of 50 patients who were included in the study with the diagnosis of chronic dacryocystitis and planned to undergo EDCR was  $42.8 \pm 7.2$  (range: 28 to 62) years. Study population consisted of 39 (78%) female and 11 (22%) male patients. Twenty-eight left and 22 right eyes were operated and 150 swab samples retrieved from conjunctiva, lacrimal sac and inferior nasal meatus were evaluated.

Among 150 swab samples, bacterial growth was detected in 136 (90.6%) and not detected in 14 (9.4%) culture samples. A total of 147 isolates were proliferated. A single

(n=125; 91.9%) or two different (n=11; 9.1%) microorganisms were grown on culture media. The distribution of gram-positive strains and gram-negative strains were (n=91; 61.90%) and (n=56; 38.10%), respectively. The distribution of the strains isolated in patients with chronic dacryocystitis is shown in Table 1.

Distribution of isolates grown in total of 150 samples retrieved before and after the operation was as follows:

- Conjunctiva (44/8): total bacterial growth in 44 samples (gram-positive 33 samples, gram-negative 11 samples) and no bacterial growth in 8 samples.

**Table 1.** Distribution of the strains isolated in patients with chronic dacryocystitis.

		Conjunctiva	Lacrimal sac	Inferior nasal meatus	Total (%)
<b>Gram-positive</b>	MSSA	9	7	13	29 (19.72%)
	MSCNS	9	9	8	26 (17.68%)
	MRCNS	6	8	7	21 (14.28%)
	MRSA	1	1	1	3 (2.04%)
	GBS	1	1	1	3 (2.04%)
	<i>Difteroid bacilli</i>	3	-	-	3 (2.04%)
	<i>S. pneumoniae</i>	2	-	-	2 (1.36%)
	<i>S. oralis</i>	1	-	1	2 (1.36%)
	<i>S. mitis</i>	1	-	1	2 (1.36%)
<b>Total gram-positive</b>		33	26	32	91 (61.9%)
<b>Gram-negative</b>	<i>P. aeruginosa</i>	1	11	4	16 (10.88%)
	<i>K. pneumoniae</i>	3	4	4	11 (7.48%)
	<i>E. coli</i>	1	1	7	9 (6.12%)
	<i>S. maltophilia</i>	2	1	-	3 (2.04%)
	<i>P. vulgaris</i>	-	2	-	2 (1.36%)
	<i>C. freundii</i>	-	1	1	2 (1.36%)
	<i>E. aerogenes</i>	-	1	1	2 (1.36%)
	<i>A. baumannii</i>	-	-	2	2 (1.36%)
	<i>E. cloacae</i>	-	2	-	2 (1.36%)
	<i>C. koseri</i>	-	1	-	1 (0.68%)
	<i>E. faecalis</i>	-	-	1	1 (0.68%)
	<i>P. stutzeri</i>	1	-	-	1 (0.68%)
	<i>S. marcescens</i>	1	-	-	1 (0.68%)
	<i>P. mirabilis</i>	-	1	-	1 (0.68%)
	<i>K. oxytoca</i>	1	-	-	1 (0.68%)
	<i>A. iwoffii</i>	1	-	-	1 (0.68%)
<b>Total gram-negative</b>		11	25	20	56 (38.10%)
<b>Total isolates</b>		44 (29.9%)	51 (34.7%)	52 (35.4%)	147 (100%)

GBS: Group B *Streptococcus*; MRCNS: methicillin-resistant coagulase-negative *Staphylococcus*; MRSA: methicillin-resistant *Staphylococcus aureus*; MSCNS: methicillin-sensitive coagulase-negative *Staphylococcus*; MSSA: methicillin-sensitive *Staphylococcus aureus*

- Lacrimal sac (51/2): total bacterial growth in 51 samples (gram-positive 26 samples, gram-negative 25 samples) and no bacterial growth in 2 samples.
- Inferior nasal meatus (52/4): total bacterial growth in 52 samples (gram-positive 32 samples, gram-negative 20 samples) and no bacterial growth (n=4).

Most frequently isolated gram-positive bacteria were methicillin-sensitive *Staphylococcus aureus* (MSSA) (n=29; 19.72%), methicillin-sensitive coagulase-negative *Staphylococci* (MSCNS) (n=26; 17.68%) and methicillin-resistant coagulase-negative *Staphylococci* (MRCNS) (n=21; 14.28 %) (Table 1). Most frequently isolated Gram-negative strains were *Pseudomonas aeruginosa* (n=16; 10.88%), *Klebsiella pneumoniae* (n=11; 7.48%) and *Escherichia coli* (n=3; 2.04%) (Table 1).

In our study, in various regions of different compartments (conjunctiva, lacrimal sac and inferior nasal meatus) the number of microorganisms (MSSA, MSCNS and MRCNS) grown, rates of bacterial proliferation in pairwise comparisons (conjunctiva - lacrimal sac, conjunctiva - inferior meatus or lacrimal sac - inferior meatus), probabilities of concurrent bacterial proliferation and correlations among them are shown in Table 2. Number of individual microorganisms grown in cultures prepared from two different regions, both separately and in combination

and distribution of each microorganism as expressed statistically as percentages are shown in Table 2.

The number of a certain microorganism grown in different compartments both individually or concurrently was also recorded (i.e. MSSA was grown in nine swab samples retrieved from conjunctiva, seven from lacrimal sac, however simultaneous proliferation of MSSA was observed in six swab samples of conjunctiva and lacrimal sac). Starting from this observation, a correlation was seen between conjunctiva and lacrimal sac as for bacterial growth.

For MSCNS and MRCNS, bacterial growth demonstrated similarities among three regions. This similarity can be explained by the correlation between growth rates of both compartments. In other words, growth of MSSA in conjunctiva was also seen in the lacrimal sac and inferior meatus; however, proliferation of MSSA in inferior meatus was not observed concurrently in the lacrimal sac (growth of MSSA was seen in the inferior meatus in 13 cases and in only seven of them lacrimal sac was infected with the same microorganism at the same time). Therefore, simultaneous growth of MSSA in these two locations was not a consistent finding.

Results were evaluated statistically using McNemar test (Table 3). In pairwise comparisons between all locations, growth of MSCNS and MRCNS demonstrated similarities. In other words, growth of these microorganisms

**Table 2.** Concurrent bacterial growth of different compartments (conjunctiva, lacrimal sac and inferior nasal meatus) and correlations among them.

Regions of isolated strains						
Gram positive	Conj.	L. sac	Conj. + L. sac	Conj. + L. sac / Conj.; %	Conj. + L. sac / L. sac; %	p-value
MSSA	9	7	6	6/9x100 = 66.6%	6/7x100 = 85.7%	p=0.002
MSCNS	9	9	6	6/9x100 = 66.6%	6/9x100 = 66.6%	p=0.003
MRCNS	6	8	5	5/6x100 = 83.3%	5/8x100 = 62.5%	p=0.003
	Conj.	Inf. nm	Conj. + Inf. nm	Conj. + Inf. nm / Conj.; %	Conj. + Inf. nm / Inf. nm; %	p-value
MSSA	9	13	7	7/9x100 = 77.7%	7/13x100 = 53.8%	p=0.004
MSCNS	9	8	5	5/9x100 = 55.5%	5/8x100 = 62.5%	p=0.003
MRCNS	6	7	6	6/6x100 = 100%	6/7x100 = 85.7%	p=0.002
	L. sac	Inf. nm	L. sac + Inf. nm	L. sac + Inf. nm / L. Sac; %	L. sac + Inf. nm / Inf. nm; %	p-value
MSSA	7	13	6	6/7x100 = 85.7%	6/13x100 = 46.1%	p=0.006
MSCNS	9	8	5	5/9x100 = 55.5%	5/8x100 = 62.5%	p=0.003
MRCNS	8	7	5	5/8x100 = 62.5%	5/7x100 = 71.4%	p=0.002

Conj.: conjunctiva bacterial proliferation; L. sac: lacrimal sac bacterial proliferation; Inf. nm: inferior nasal meatus bacterial proliferation; Conj. + L. sac: conjunctiva bacterial proliferation and lacrimal sac bacterial proliferation in both regions; Conj. + Inf. nm: conjunctiva bacterial proliferation and inferior nasal meatus bacterial proliferation in both regions; L. sac + Inf. nm: lacrimal sac bacterial proliferation and inferior nasal meatus bacterial proliferation in both regions; MRCNS: methicillin-resistant coagulase-negative *Staphylococcus*; MSCNS: methicillin-sensitive coagulase-negative *Staphylococcus*; MSSA: methicillin-sensitive *Staphylococcus aureus*

in one location points to their proliferation in the other location or vice versa.

Simultaneous growth of MSSA was observed in pairwise comparisons between conjunctiva - lacrimal sac and conjunctiva - inferior meatus; however, metachronous growth of MSSA was noted between lacrimal sac and inferior meatus. MSSA was localized concurrently in conjunctivas and lacrimal sacs of our patients, while such a correlation was not detected between lacrimal sac and inferior meatus as for growth of MSSA. This observation suggests us that MSSA may proliferate only in the lacrimal sac but not in the inferior meatus or vice versa.

Complications of chronic dacryocystitis such as conjunctivitis, corneal ulcer, acute on chronic dacryocystitis, lacrimal abscess and fistula were seen in 17 (34%) of these patients; 76 (51.7%) of the culture samples were positive for bacterial growth.

Antimicrobial susceptibility test results for gram-positive and gram-negative isolates are shown in Tables 4 and 5, respectively.

All gram-positive isolates were susceptible to vancomycin, teicoplanin and linezolid. Among gram-negative isolates, strains of *Enterobacteriaceae spp.* were susceptible to carbapenems, third-generation cephalosporins and cefepime. *Pseudomonas aeruginosa* strains were susceptible to meropenem (86.4%), imipenem (54.5%), aminoglycosides (90.9%).

## Discussion

Microbial flora of the ocular surface consists primarily of gram-positive microorganisms namely *Staphylococci* and

**Table 3.** Individual strains grown in cultures prepared from two different regions.

Gram-positive	Localizations	p-value*
MSSA	Conjunctiva and lacrimal sac	p=0.002
	Conjunctiva and inferior nasal meatus	p=0.004
	Lacrimal sac and inferior nasal meatus	p=0.06
MSCNS	Conjunctiva and lacrimal sac	p=0.003
	Conjunctiva and inferior nasal meatus	p=0.003
	Lacrimal sac and inferior nasal meatus	p=.003
MRCNS	Conjunctiva and lacrimal sac	p=0.003
	Conjunctiva and inferior nasal meatus	p=0.002
	Lacrimal sac and inferior nasal meatus	p=0.002

\*McNemar test: p<0.005 significant. **MRCNS:** methicillin-resistant coagulase-negative *Staphylococcus*; **MSCNS:** methicillin-sensitive coagulase-negative *Staphylococcus*; **MSSA:** methicillin-sensitive *Staphylococcus aureus*

diphtheroids. *S. aureus*, is the most frequently isolated bacteria in eye infections. Microorganisms found in conjunctival flora can be transformed into pathogens and become a source of infection in the presence of predisposing conditions including ophthalmic surgery, immunosuppression, malnourishment and lacrimal duct obstruction.<sup>[1-4]</sup>

Coden et al.<sup>[3]</sup> analyzed purulent discharge coming from lacrimal sac during dacryocystorhinostomy operations performed on the patients diagnosed as dacryocystitis and detected bacterial growth in 52.5% of the cases. Based on culture results, growth of a single or mixed bacteria was detected in 71 and 29% the cases, respectively. Growth of gram-positive (64.5%) and gram-negative

**Table 4.** Antibiotic susceptibility of gram-positive isolates.

Isolates	Antibiotic susceptibility										
	Gram-positive	PEN	VA	TEIKO	LZD	E	DA	LEV	SXT	FA	GN
MSSA (n=29)		9.1%	100%	100%	100%	100%	100%	100%	100%	100%	100%
MSCNS (n=26)		24.1%	100%	100%	100%	55.1%	55.1%	96.5%	82.7%	27.5%	96.5%
MRCNS (n=21)		0%	100%	100%	100%	17.8%	17.8%	32.1%	60.7%	10.7%	32.1%
MRSA (n=5)		0%	100%	100%	100%	20%	20%	100%	100%	100%	100%
GBS (n=4)		100%	100%	100%	100%	100%	100%	100%	100%	0%	0%
<i>S. mitis/oralis</i> (n=2)		0%	100%	100%	100%	0%	0%	100%	0%	0%	0%
<i>S. pneumoniae</i> (n=2)		0%	100%	100%	100%	0%	0%	100%	0%	0%	0%

DA: clindamycin; E: erythromycin; FA: fusidic acid; GBS: Group B *Streptococcus*; GN: gentamycin; LEV: levofloxacin; LZD: linezolid; MRCNS: methicillin-resistant coagulase-negative *Staphylococcus*; MRSA: methicillin-resistant *Staphylococcus aureus*; MSCNS: methicillin-sensitive coagulase-negative *Staphylococcus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; PEN: penicillin; SXT: trimethoprim-sulfamethoxazole; TEC: teicoplanin; VA: vancomycin.



**Table 5.** Antibiotic susceptibility results of gram-negative microorganisms.

Isolates	Antibiotic susceptibility											
	AMP	AMC	CAZ	CRO	TZP	SCF	AK	GN	FEP	IMP	MEM	SXT
<i>E. coli</i> (n=14)	57.1%	92.8%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>K. pneumoniae</i> (n=15)	33.3%	91.6%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>P. vulgaris</i> (n=1)	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
ESBL (+) <i>P. vulgaris</i> (n=2)	0%	0%	0%	0%	100%	100%	100%	100%	0%	100%	100%	100%
	CAZ	FEP	TZP	SCF	AK	GN	IMP	MEM	CIP			
<i>A. baumannii</i> (n=3)	33.3%	66.7%	33.3%	66.7%	66.7%	66.7%	66.7%	66.7%	66.7%			
<i>P. aeruginosa</i> (n=22)	90.9%	81.6%	77.2%	86.4%	90.9%	90.9%	54.5%	86. %4	51%			
<i>P. stutzeri</i> (n= 1)	100%	100%	100%	100%	100%	100%	100%	100%	100%			
<i>C. koserii</i> (n=2)	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>E. aerogenes</i> (n=3)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>S. maltophilia</i> (n=3)	100%	0%	100%	100%								
	AMP	AMC	CAZ	CRO	TZP	SCF	AK	GN	FEP	IMP	MEM	SXT
<i>S. marsecens</i> (n=1)	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>K. oxytoca</i> (n=2)	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>E. cloacae</i> (n=2)	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>A. iwoffii</i> (n=1)	100%	100%	100%	100%	100%	100%	100%	100%	100%			
<i>C. freundii</i> (n=3)	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
<i>P. mirabilis</i> (n=1)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

AK: amikacin; AMC: amoxicillin-clavulanic acid; AMP: ampicillin; CAZ: ceftazidime; CIP: ciprofloxacin; CRO: ceftriaxone; FEP: cefepime; GN: gentamycin; IMP: imipenem; MEM: meropenem; SCF: sulbactam/cefoperazone; SXT: trimethoprim-sulfamethoxazole; TZP: tazobactam/piperacillin.

(27.3%) was also observed. The most prevalent gram-positive bacteria were *Staphylococcus epidermidis* (27.3%) and *Staphylococcus aureus* (22.1%) while *Pseudomonas aeruginosa* (8.7%) was observed most commonly among gram-negative bacteria. Microbiological results of culture samples retrieved from conjunctivas or lacrimal sacs of the patients diagnosed as chronic dacryocystitis and frequently observed pathogenic agents during the last decade are shown in Table 6.<sup>[4,8-14]</sup> In the studies included in Table 6, microbiology reports of culture samples retrieved from conjunctival irrigation fluid or lacrimal sac discharge, indicated predominance of gram-positive bacteria in 53.7 and 77.4% of the cases, respectively. Among gram-positive microorganisms, *Staphylococci spp.* were grown most frequently (in order of decreasing frequency, *S. aureus* [24.6–53.8%] and *S. epidermidis* [26.1–45.3%]). Besides, in various publications, culture samples were harvested using various methods including conjunctival or punctal irrigation, aspiration or from lacrimal sac as a direct swab sample during operation.<sup>[4,8-14]</sup> In our study, a total number of 150 swab samples were retrieved from conjunctiva, infe-

rior nasal meatus and intraoperatively from lacrimal sac all under sterile conditions. In 136 (90.6%) samples, bacterial growth was detected and in 14 (9.4%) samples, any bacterial growth was not observed. In 125 (91.9%) locations growth of a single microorganism and in 11 (9.1%) regions mixed bacterial growth (two different bacteria) were observed and a total of 147 isolates were grown. Bacterial isolates consisted mostly of gram-positive (n=91 samples; 61.90%) and gram-negative (n=56 samples; 38.10%) microorganisms which was in compliance with the literature results. Culture results of the samples retrieved from conjunctiva, inferior meatus of the nasal cavity and intraoperatively from lacrimal sac demonstrated similarities with the results of the comparable literature studies. However, our results differed from the outcomes of the studies which evaluated all of these locations in combination. Culture results of the patients operated with the diagnosis of chronic dacryocystitis demonstrated that among gram-positive group, *Staphylococci* took the first place (53.72%). Among subgroups of *Staphylococci spp.*, growth of *S. aureus* (21.76%) was mostly observed.

**Table 6.** Microbiological results of culture samples retrieved from conjunctivas or lacrimal sacs of the patients diagnosed as chronic dacryocystitis during the last ten years.

	Patients	Sample region	Microbiological results
Kubo et al. <sup>[8]</sup>	1 AD 3 CD	Conjunctival fornix irrigation, nasal cavity lacrimal sac.	MRSA
Sun et al. <sup>[9]</sup>	91 CD	Conjunctival, lacrimal sac refluxing material	Gr+ (64.4%); Gr- (18.9%) Most common: <i>Staphylococcus epidermidis</i> (26.1%)
Chaudhry et al. <sup>[10]</sup>	188 CD	Conjunctival fornix irrigation, or EDCR lacrimal sac culture	Gr+ (53.7%); Gr- (25.8%) Most common: <i>Staphylococcus epidermidis</i> (33.5%)
Mills et al. <sup>[4]</sup>	21 AD 68 CD	Lacrimal sac, intraoperative or needle aspiration/stab incision sac reflux.	Chronic dacryocystitis Gr+ (68.8%); Gr- (28.7%) Most common: <i>Staphylococcus aureus</i> (24.6%)
Das et al. <sup>[11]</sup>	421 CD	External DCR lacrimal sac	Gr+ (75%); Gr- (25%) Most common: <i>Staphylococcus epidermidis</i> (40.6%)
Bharathi et al. <sup>[12]</sup>	566 AD 1325 CD	Conjunctival, DCR lacrimal sac culture	Chronic dacryocystitis Gr+ (70.9%); Gr- (29.1%) Most common: <i>Staphylococcus aureus</i> (44.2%)
Razavi et al. <sup>[13]</sup>	12 AD 49 CD	Positive regurgitation	Chronic dacryocystitis Gr+ (77.4%); Gr- (18.9%) Most common: <i>Staphylococcus epidermidis</i> (45.3%)
Kim et al. <sup>[14]</sup>	33CD	External or endoscopic DCR surgery silicone tube	Gr+ (73.1%); Gr- (23.1%) Most common: <i>Staphylococcus aureus</i> (53.8%)

AD: acute dacryocystitis; CD: chronic dacryocystitis; DCR: dacryocystorhinostomy; MRSA: methicillin-resistant *Staphylococcus aureus*

Mills et al.<sup>[4]</sup> reported a multi-centered study in 6 different centers and collected 80 culture samples from 21 (23.6 %) patients with acute and chronic (n=68; 76.4%) infections in a study population of 89 patients and gram-positive and gram-negative isolates were grown in 55 (68.8%) and 23 (28.7%) culture samples, respectively. In the group of chronic dacryocystitis, gram-positive (64.9%; 37/57) and gram-negative (31.6%; 18/57) microorganisms were grown and in the gram-positive group, *Staphylococcus aureus* (24.6%), MSSA (22.8%), MRSA (1.8%) and coagulase-negative *Staphylococci* (17.5%) were identified most frequently. Kim et al.<sup>[14]</sup> implanted silicone tubes in 89 patients using external method (n=34) or EDCR (n=5) procedure and obtained culture samples from all of these 89 cases. They had identified a total of 52 isolates from 37 (94.9%) cases with significant culture results. These isolates consisted of gram-positive (73.1%) and gram-negative (23.1%) bacteria. Most frequently, *Staphylococci* (53.8%) were grown in cultures. Among gram-positive microorganisms, 28 strains of *S. aureus*, MRSA and CNS were identified in 78.6% (n=22) and 7.7% of the cases, respectively.

Relevant with results of the literature, bacterial colonization which took place following partial or total occlusion of the lacrimal drainage system in cases diagnosed as chronic dacryocystitis led to chronic infection and growth of gram-positive bacteria with a dominance of *S. aureus*. In our study, distribution of gram-positive microorganisms in order of decreasing frequency was as follows: MSSA - 19.72%, MSCNS - 17.68%, MRCNS - 14.28%, and MRSA - 2.04%

Culture results of the samples harvested regionally from conjunctiva, lacrimal sac and inferior meatus, synchronicity and concordance between growth of MSSA, MSCNS and MRCNS in pairwise comparisons (conjunctiva - lacrimal sac, conjunctiva - inferior meatus and lacrimal sac - inferior meatus) were analyzed and based on the results of the statistical analysis, growth of MSCNS and MRCNS demonstrated similarities in all three regions of growth with statistically significant outcomes (i.e. growth of MSSA was seen in inferior meatus in 13 cases and in seven of these cases, MSSA was also detected concurrently in culture samples retrieved from lacrimal sac). Therefore, a metachronism between these two locations as for growth of MSSA is the point in question. According to

McNemar test, synchronous growth of MSCNS and MRCNS was observed in pairwise comparisons of all locations. In other words, this result indicates simultaneous growth of these bacteria in both locations or vice versa. However, growth of MSSA demonstrated synchronicity between conjunctiva and lacrimal sac and also between conjunctiva and inferior meatus, while metachronous growth of MSSA was observed between lacrimal sac and inferior meatus. In other words, MSSA may proliferate in the lacrimal sac, but not in the inferior meatus or vice versa. In conclusion, based on the gram-positive culture results of the samples retrieved from patients who underwent EDCR operations with the indication of chronic dacryocystitis, distribution of frequencies of MSSA, MSCNS and MRCNS among compartments were compared, and growth of MSCNS and MRCNS showed synchronicity in all three regions while growth of MSSA was in concordance only between conjunctiva and lacrimal sac or inferior meatus but not between lacrimal sac and inferior meatus.

Diseases of the nasolacrimal system are generally chronic in nature and recurrent episodes of conjunctivitis and dacryocystitis occur in almost all patients. Antimicrobial prophylaxis is needed in lacrimal surgery. During the post-operative period of EDCR surgery, broad-spectrum antibiotics are used for 5–7 days. As an oral antibiotic, generally 3rd generation fluoroquinolons or extended-spectrum penicillin derivatives (cephalosporins, amoxicillin/clavulanic acid) are preferred.<sup>[15–18]</sup> In our study, all gram-positive isolates were susceptible to vancomycin, teicoplanin and linezolid. Besides, 96–100% of the microorganisms –excluding MRCNS– are susceptible to levofloxacin. Among gram-negative isolates, strains of *Enterobacteriaceae spp.* were susceptible to carbapenems. *Pseudomonas aeruginosa* strains were susceptible to meropenem (86.4%), imipenem (54.5%), and aminoglycosides (90.9%).

## Conclusion

Obstruction of the nasolacrimal system is generally a chronic condition and in all of these patients recurrent attacks of conjunctivitis and dacryocystitis occur. In lacrimal surgery, antimicrobial prophylaxis is frequently required. In our study, culture results of the samples retrieved from conjunctiva, inferior meatus of the nasal cavity and intraoperatively from lacrimal sac demonstrated similarities with the results of the comparable literature studies. However, our results differed from the outcomes of the studies which evaluated all of these locations in combination. Culture results of the patients operated with

the diagnosis of chronic dacryocystitis demonstrated that *Staphylococci* took the first place (53.72%) among gram-positive group. Among subgroups of *Staphylococci spp.*, the growth of *S. aureus* (21.76%) was observed most commonly. With the results obtained, we have offered guiding alternatives for the selection of appropriate antibiotics to the clinicians who are caring for cases monitored with the diagnosis of chronic dacryocystitis.

**Conflict of Interest:** No conflicts declared.

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# Incidence of occult lymph node metastasis in patients with head and neck cancer

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## Abstract

**Objective:** The objective of the study is to determine the incidence of occult lymph node metastasis detected in patients with head and neck cancer who applied to our clinic.

**Methods:** Medical files of 107 patients who had been diagnosed as head and neck cancer between 2007 and 2012 were retrospectively examined. The patients who were accepted as N0 both clinically and radiologically at the time of diagnosis and those who had undergone neck dissection in addition to the treatment of primary tumor were included in the study. The patients were grouped based on the diagnosis of the primary tumor. Histopathology results of the patients and those with lymph node metastasis were documented. The proportion of the patients with occult lymph node metastases was calculated and primary tumor sites with a higher probability of occult lymph node metastases were determined.

**Results:** A total of 64 patients were included in the study who were diagnosed as laryngeal (n=42; 65.6%), oral cavity (n=15; 23.4%), parotid gland (n=5; 7.8%), nasal cavity (n=1; 1.5%) and auricular (n=1; 1.5%) carcinomas. Histopathologically lymph node metastases were detected in patients with laryngeal (n=12; 70.5%), oral cavity (n=4; 23.5%) and parotid gland (n=1; 5.8%) carcinomas. Laryngeal cancers were subdivided into supraglottic (n=4), transglottic (n=7) and glottic (n=1) cancers. The highest rate of metastasis was detected in patients with transglottic laryngeal carcinoma.

**Conclusion:** Occult lymph node metastasis is an important issue which should be kept in mind in cases with head and neck cancers. Location of primary tumor is an effective influential factor concerning this issue. As a result of this study, we thought that occult lymph node metastases are frequently seen in patients with transglottic laryngeal cancers.

**Keywords:** Head and neck carcinoma, neck dissection, occult lymph node metastasis.

## Özet: Baş ve boyun kanserli hastalarda gizli lenf nodu metastazı insidansı

**Amaç:** Bu çalışmanın amacı kliniğimize başvuran baş-boyun kanserli hastalarda saptanan gizli lenf nodu metastazı oranını belirlemektir.

**Yöntem:** Kliniğimizde 2007 ile 2012 tarihleri arasında baş ve boyun kanseri tanısı alan 107 hastanın dosyası retrospektif olarak incelendi. Tanı anında klinik ve radyolojik olarak N0 kabul edilen ve primer tümörün tedavisine ek olarak boyun diseksiyonu yapılan hastalar çalışmaya dâhil edildi. Hastalar primer tümör tanısına göre gruplandırıldı. Hastaların patoloji sonuçları dokümanete edildi ve lenf nodu metastazı olan hastalar tespit edildi. Gizli lenf nodu metastazına sahip hastaların oranı hesaplandı ve gizli lenf nodu metastazı ihtimali yüksek olan primer tümör bölgeleri belirlendi.

**Bulgular:** Çalışmamıza dahil edilen toplam hasta sayısı 64'tür. Altmış dört hastanın 42'si (%65.6) larenks, 15'i (%23.4) oral kavite, 5'i (%7.8) parotis bezi, 1'i (%1.5) nazal kavite, geri kalan 1'i (%1.5) ise aurikula kanseri tanısı olan hasta idi. Larenks kanseri olan 12 (%70.5) hastada (4'ü supraglottik, 7'si transglottik ve 1'i glottik), oral kavite kanseri olan 4 (%23.5) hastada ve parotis kanseri olan 1 (%5.8) hastada histopatolojik olarak lenf nodu metastazı mevcut idi. Larenks kanseri, supraglottik (n=4), transglottik (n=7) ve glottik (n=1) alt gruplarına ayrılmaktaydı. En yüksek gizli lenf nodu metastaz oranı transglottik larenks kanserinde tespit edildi.

**Sonuç:** Baş boyun kanserlerinde gizli lenf nodu metastazı akıldta tutulması gereken önemli bir konudur. Bu konuda önemli etkili husus ise primer tümörün lokalizasyonudur. Bu çalışma sonucunda transglottik larenks kanserlerinde gizli lenf nodu metastaz oranının yüksek olduğunu düşünüyoruz.

**Anahtar sözcükler:** Baş ve boyun kanseri, boyun diseksiyonu, gizli lenf nodu metastazı.

The incidence of occult lymph node metastasis in patients with clinically and radiologically N0 head and neck cancers ranges between 4 and 40 percent.<sup>[1]</sup> In these cancer patients,

number, location and extent of lymph node metastasis are important issues in accurate planning of the treatment, prediction of patient's prognosis and evaluation of treatment

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response. Increased incidence of lymph node metastases enhances the probability of local recurrence and remote metastases and decreases survival rates nearly 50 percent.<sup>[2]</sup>

The incidence of lymph node metastasis changes with characteristics and location of primary tumor. In the present study, the frequency of occult lymph node metastasis has been determined during the diagnostic process of the patients with head and neck N0 cancers who had received surgical treatment.

### Materials and Methods

Medical files of 107 patients with head and neck cancer who applied to the polyclinics of Ear-Nose and Throat Department between the years 2007 and 2012 were retrospectively analyzed. At the time of diagnosis, patients in whom metastatic lymph nodes were not detected during otorhinolaryngological examinations, neck ultrasound (US) and neck computed tomography (CT) and had undergone neck dissection in addition to the treatment of the primary tumor were included in the study. The patients were grouped based on the location of the primary tumor. Patients with laryngeal cancer were divided into groups of supraglottic, glottic and transglottic cancer. The incidence rates of the patients with preoperatively accepted as N0 in TNM classification but had revealed lymph node metastasis in postoperative histopathological examination were determined. Locations of primary tumors with higher percentage of occult lymph node metastases were documented.

### Results

In preoperative TNM classification, 64 (8 women and 56 men) patients with a mean age of 59.8±9.8 (range: 34 to 79) years who were radiologically and clinically accepted to be in stage N0 according to preoperative TNM classification were included in the study. Primary tumor was localized in larynx (n=42; 65.6%), oral cavity (n=15; 23.4%), parotid gland (n=5; 7.8%), nasal cavity (n=1; 1.5%) and auricula (n=1; 1.5%) (Fig. 1).

In postoperative evaluation 17 (26.5%) of a total 64 patients, pathological lymph nodes were detected. In 12 (70.5%) of these 17 patients primary tumor was localized in larynx (n=12; 70.5%), oral cavity (n=4; 23.5%) and parotid gland (n=1; 5.8%). Among 12 patients with laryngeal cancer, cases with supraglottic (n=4), transglottic (n=7) and glottic (n=1) cancer were detected. In 4 patients with oral cavity cancers, primary tumor was localized in tongue in 3 and base of the oral cavity in 1 patient. When

patients with occult lymph node metastases were grouped within themselves, the highest rate (70.5%) of lymph node metastases was detected in laryngeal cancer group and in transglottic laryngeal cancer (41.1%) in this group (Fig. 2).

When patients included in the study group were analyzed within their own subgroups, since in 12 out of a total 42 patients with laryngeal cancer lymph node metastases

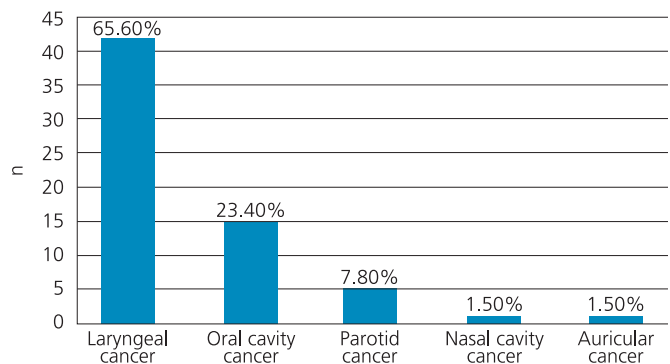


Fig. 1. Percentages of the patients considered to be in stage N0.

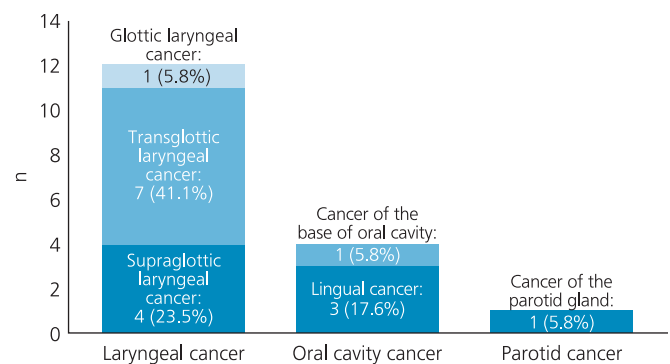


Fig. 2. Percentages of the patients with lymph node metastases.

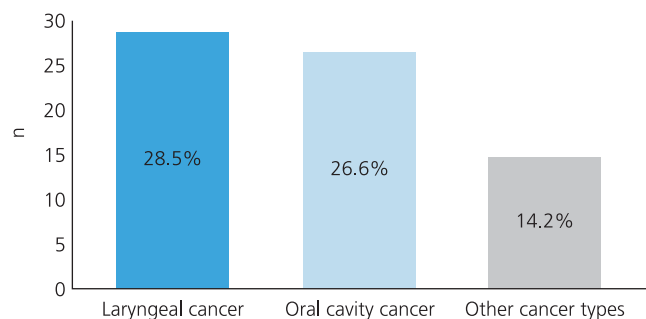


Fig. 3. Percentages of the patients with occult lymph node metastases.

were detected, the rate of occult lymph node metastases was detected as 28.5 percent. While 4 out of 15 patients with oral cavity cancers lymph node metastases were detected, so the rate of occult lymph node metastasis was estimated as 26.6 percent. In other patients (parotid gland, nasal cavity and auricular cancer) the corresponding rate was found to be 14.2 percent (Fig. 3).

## Discussion

In patients with head and neck cancer, accurate evaluation of lymph node metastases during preoperative period effects treatment method to be performed and prognosis of the patient. In a study performed by Cerezo et al., 5-year survival rates in patients with only one lymph node metastasis was found to be 41%, while in patients with 2 or  $\geq 3$  lymph node metastases it was 22 percent.<sup>[3]</sup>

Knowing the group of patients with higher rates of occult lymph node metastases can aid in determination of type of lymph node dissection in the planning of surgery and/or specification of radiotherapy application field. This issue is crucial especially in patients who during preoperative period had been clinically and radiologically accepted as N0 patients. Literature reviews demonstrate that the incidence of occult metastases ranges between 15 and 20 percent.<sup>[4]</sup> Also in our study this rate was detected as 28.5% in accordance with literature findings. In a study by Woolgar performed on oral cavity cancers, the authors detected occult lymph node metastases in 21% (n=32) of 152 patients with N0 stage oral cavity cancers.<sup>[5]</sup> In our study in 4 (26.6%) of 15 patients with N0 oral cavity cancers occult lymph node metastases were detected. In a study by Pillsbury et al.,<sup>[6]</sup> the incidence rates of occult lymph node metastases were 36% in transglottic, 13% in glottic and 25.6% in supraglottic laryngeal cancers, and 29% in oral cavity cancers. In line with these results, the

highest rate of occult lymph node metastases was determined in transglottic laryngeal cancers, followed by oral cavity cancers. In our study, the highest rate of occult lymph node metastases was detected in patients with transglottic laryngeal cancers, followed by supraglottic laryngeal cancers and oral cavity cancers in decreasing order of frequency. This discrepant outcome of our study was thought to be related to the scarce number of patients with oral cavity cancers.

In conclusion, as seen in studies performed and in our study, the rate of occult lymph node metastases is closely related to the primary tumor site. Therefore especially in transglottic laryngeal cancers and oral cavity cancers occult lymph node metastases are seen at higher rates we recommend addition of prophylactic lymph node dissection to the treatment plan of the patients.

**Conflict of Interest:** No conflicts declared.

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## Efferescent tablets: a safe and practical delivery system for drug administration

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### Abstract

Efferescence is defined as the evolution of gas bubbles from a liquid as a result of a chemical reaction. For medicinal use, efferescent tablets have specific characteristics that allow rapid adsorption of the intended drug. In this manner, a medication can be absorbed easily and effectively if it dissolves easily in water and is present at a sufficient dose. Common acids utilized for efferescent reactions are citric, malic, tartaric, adipic and fumaric acids. Citric acid is most commonly used for this application, which also adds a citrus-like taste to the products. Tartaric, adipic and fumaric acids are usually used in small amounts, due to their low water solubility. Efferescent tablets are used to simplify the handling of doses, provide optimal compatibility, promote superior and rapid absorption, increase a patient's liquid intake and circumvent the difficulty of swallowing large pills. This review defines efferescent tablets in terms of the technology and describes the advantages and disadvantages.

**Keywords:** Efferescent, tablet, advantages, disadvantages.

### Özet: Eferesan tabletler: ilaç kullanımı için güvenli ve pratik bir uygulama sistemi

Eferesans, bir sıvı içinde oluşan kimyasal reaksiyon sonucu, çözünme ve gaz kabarcıklarının oluşması olarak tarif edilmektedir. Tıbbi kullanımda eferesan tabletler, verilen ilacın hızlı emilimini sağlamaya yönelik bir özellik taşımaktadır. Verilen ilaç, eğer su içinde yeterli dozda ve kolayca çözünürse daha hızlı ve etkin şekilde emilim sağlanacaktır. Köpürme reaksiyonu için genellikle sitrik, malik, tartarik, adipik veya fumarik asitler kullanılmaktadır. En sık tercih edilen, ürüne hafif bir limon aroması da veren sitrik asittir. Tartarik, adipik ve fumarik asitler, suda çözünürlükleri daha düşük olduğu için daha az miktarlarda kullanılırlar. Uygun ilaç dozu alınımın sağlanması, ilaca uyumun kolaylaştırılması, hızlı ve daha iyi emilim, hastanın sıvı alımının artırılması ve büyük tabletlerin yutulma zorluğunun ortadan kaldırılması için eferesan tabletler kullanılmaktadır. Bu derlemede, teknolojik açıdan eferesan tabletler değerlendirilmiş, avantaj ve dezavantajları tanımlanmıştır.

**Anahtar sözcükler:** Eferesan, tablet, avantaj, dezavantaj.

Medications such as pills are the forms generally used, whereas they have some disadvantages. Slow absorption is the important disadvantage as the onset of action gets pro-

longed. In liquid forms of the medication, the delay is avoided. Many drugs do not have enough stability levels in the suspension form. Gastric residence also affects drug delivery

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which is predicted before. Gastro-retentive preparations are created to manage gastric residence. Another form of the drugs is effervescent tablets.<sup>[1]</sup> Effervescent mixtures and powders, and compound effervescent powders including saline cathartics are also used.<sup>[2]</sup>

In effervescent technology, gas bubbles occur from the liquid after chemical reaction. Alkali metal bicarbonates and acids (mainly citric or tartaric) are used to make effervescence. The reaction occurs after adding water.<sup>[3-5]</sup> The main issue is acid-base reaction. The basic component is sodium bicarbonate and acidic component is citric acid.<sup>[5]</sup>

Effervescent tablets have specific characteristics that allow rapid adsorption of the drug. The drug can be absorbed easily when it displays adequate dissolution in water and is present at a sufficient dose.<sup>[6]</sup> Potassium citrate has these characteristics. In case of kidney stones containing urate and calcium, Potassium citrate is used which is helpful to decrease the prevalence of the stones.<sup>[7]</sup> Patients with kidney stones should take too much water to use effervescent easily. Potassium citrate powders are given with packages and the dose is measured. Therefore, a study has been aimed to design and formulate potassium citrate effervescent tablets. They decrease calcium oxalate and urate stones.<sup>[8]</sup>

### Definition of Effervescent Tablets

The chemical reaction occurs in effervescent tablets. It is related to acid-base reaction. At the end, carbon dioxide is released. Tartaric, malic, fumaric, citric and adipic acids are utilized. Due to the citrus-like taste, citric acid is usually preferred for effervescent. Malic acid is expensive, whereas it adds smoother taste. The low water-soluble agents are fumaric, malic and tartaric acids. So, they can be consumed in small amounts.<sup>[9]</sup>

In effervescent technology, when organic acid and bicarbonate get together in the water, carbon dioxide is released. The solving process is seen in 17–20°C water. They may be easily carried and used. Their taste is pleasing. The foam of them helps to kill the local bacteria. In traditional Chinese Medicine, similar techniques and materials are used to prepare similar medicine.<sup>[10]</sup>

After the reaction of effervescent tablets, simultaneous carbon dioxide is produced. Their contents are compressed mixture of acids and sodium bicarbonate.<sup>[11]</sup> They rapidly dissolve in the water. When the patients have problem with capsule or tablet swallowing, these agents can be used easily.<sup>[12,13]</sup> These tablets are also absorbed faster.<sup>[14]</sup> The main acid used is citric acid. The other acids

of adipic, tartaric, malic and fumaric are also used. Alkali sources are Potassium carbonate and bicarbonate, and sodium carbonate and bicarbonate. When considering low cost, high solubility and intensity of reaction, sodium carbonate is preferred.<sup>[15]</sup> Excipients, water-soluble lubricants and colors, flavorings and sweeteners are also added.<sup>[15]</sup>

Polyvinylpyrrolidone (PVP) is used as binder in effervescent. Its form is as dry powder or wet forms of aqueous or hydroalcoholic solutions. Mannitol and PEG 6000 are other effective binders.<sup>[15,16]</sup> When using tablet press machine, relative humidity should be low ( $\leq 25\%$ ) and temperature should be at room temperature (25°C).<sup>[5]</sup> To obtain excellent flowability, production is made by direct compression method. Size of the particles should be equal. In granules, particle size should be small.<sup>[13,17]</sup> To achieve agglomeration of the particles, monohydrate citric acid is released in the fusion method (at 54°C). Using a nonreactive solution, such as ethanol or isopropanol, granulation is achieved. 0.1–0.5% water is enough for active solution.<sup>[15]</sup> The control of effervescent tablets is performed by conventional similar tablets. The control parameters are weight, hardness, pH, solution time and friability.<sup>[8,15]</sup>

Potassium citrate is soluble in water, but insoluble in alcohol.<sup>[7]</sup> It is used in metabolic acidosis and replaces sodium bicarbonate. It can also be used in urinary tract infections as an alkalizing agent. It decreases the formation of kidney stone induced by calcium oxalate and urate.<sup>[18-21]</sup> Therefore, oral supplements with potassium citrate prevent hyperkalaemia, because it can be absorbed from gastrointestinal tract highly.<sup>[8,21]</sup>

Effervescent tablet solution was compared with standard tablets in 242 patients. The formulations contained 1000 mg acetaminophen. The patients had moderate or severe pain due to the dental surgery. Both of them were evaluated in terms of pain intensity and relief. They were both effective compared to placebo. Onset of analgesia was 20 min in effervescent tablet and 45 min in standard tablet. Median pain relief time was 15 min faster in the effervescent tablet.<sup>[22]</sup>

Recently, effervescent antibiotics have been launched on the market. Consumption of the drug as a half glass of liquid seems easier than swallowing a large tablet. Particularly in patients with a sore throat or swallowing disorder, this delivery method improves the quality of life with easier and faster uptake of the drug. Furthermore, effervescent tablets have storage advantages for keeping the drug dry, stable and safe compared with syrup or suspension forms.

## Effervescent Tablet Technology

The technology of the effervescent tablets was based on chemical reaction. Acid neutralize a carbonate salt. At the end, carbon dioxide gas is released which produce the fizzing.<sup>[23]</sup> To initiate the reaction, water is important. If there is no water in the medium, acid or carbonate cannot dissociate and the reaction cannot be initiated. After the reaction begins, more water is generated. Effervescent tablets should be produced in optimum environment and packaged carefully. Therefore, stability is created. During the production, anhydrous raw materials are used. They should be kept in dry environment. Relative humidity ratio must be less than 10%. In effervescent tablets, the source of carbon dioxide is carbonate. Sodium carbonate and bicarbonate are the commonly used carbonate salts.<sup>[23]</sup>

In sodium carbonate, CO<sub>2</sub> percentage is lower than bicarbonate. In bicarbonate, CO<sub>2</sub> proportion is higher than soda ash. Its' reaction time is more quickly and it is less stable. In most of the products, both carbonate and bicarbonate are used in 50/50 ratio. Reaction time and stability are acceptable in this form. In effervescent products, magnesium and potassium carbonate are also used. Acids are the other and important part in effervescent which react with carbonates.<sup>[23]</sup> Citric acid is a trivalent and has good neutralizing effect. Fumaric acid is a divalent and more effective than citric acid. Fumaric acid reacts slowly and less soluble than citric acid. Stability of the fumaric acid is more than citric acid. The other acids are malic acid and adipic acid.<sup>[23]</sup> The weight ratio of the acid and total carbonate is 1:1 for ideal for effervescent. When this ratio is 1:10, the system will be highly soluble and reactive. Essential oils and fragrances are included as 0.5–3% in effervescent. The oil should not contain glycol solvents which can cause instability.<sup>[23]</sup>

Dyes or lake pigments can be added to produce colored solutions or products. Color stability is also important. They should be chosen as anhydrous material. Dried flower bud, herbs, chamomile extract maybe used for this purpose. The percentage may be lower than 1–2%. Another 0.1–2% of the effervescent should be consisted of vitamin E, squalene, almond oil and cosmetic esters. Foamers are surfactants. PEG-30 castor oil, laureth 4, polysorbate 80 or 85 are emulsifiers.<sup>[23]</sup>

Polymers are added as 0.2–4 percentage. PEG or polyquaternium are usually used. For solid effervescent tablets, binders are used as 10–20% (maltodextrin, lactose and sorbitol). The materials that help flowing are calcium silica, talc, fumed silica or cornstarch.<sup>[23]</sup> Production is completed with exact ratios of different materials.<sup>[3]</sup>

During production, hygroscopic materials are used to absorb moisture. Moisture may cause effervescent reaction. The production is performed in closed systems and ended by split valve technology. To achieve high level safety, low moisture should be present in ventilated air.<sup>[3]</sup>

### Granulation and drying

The tablets are produced as equal weight and homogeneous. They compressed in high-speed rotary presses. Wet granulation is avoided, because it may initiate reaction.<sup>[3]</sup> Roller compaction and direct compression are used for drying.<sup>[2]</sup> Ventilation of the machines is also controlled.<sup>[3]</sup>

### Wet granulation

The wet granulation is performed by two steps. Initial step is done by alkaline or acid components, subsequently dry blending is performed.<sup>[2]</sup> A high shear granulator is used for drying.<sup>[2]</sup> These methods need running time and cleaning processes. This is a critical step and homogeneity of the tablets is obtained with this method.<sup>[3]</sup>

### Organic solvents

Effervescent reaction is not started in inorganic solvents. These agents are used as a granulation fluid. In this method, evaporation occurs at lower heat. Drying is obtained at lower temperatures. The fluid bed is necessary because of created organic gas and non-condensable process.<sup>[3]</sup>

### Water

Water is used as a granulation fluid. It is used in very small amount, because water may initiate pre-effervescent reaction. In this reaction, carbon dioxide is released. Drying process of the production reduces the water amount. A high shear granulator is used for this purpose. In larger bath sizes, the drying time takes longer.<sup>[3]</sup> For drying, microwave technology or batches (small or medium) are used. In larger batches, the process takes more time.<sup>[3]</sup>

### Fluid bed spray granulation

In this process, simultaneous granulation and drying are performed. Low moisture levels are obtained and the risk of pre-effervescent reaction is limited to minimum. For more granulation fluid, it is necessary to have high shear process.<sup>[3]</sup>

### Lubricants

After granulation, lubricant should be added to the tablets. To improve flowing, magnesium stearate is used. It prevents tablets from sticking. When magnesium stearate is used, a film will be present on the water after dissolving of



the tablets. L-leucine plus polyethylene glycol mixture are also used for this purpose.<sup>[4,5]</sup>

### Tablet compression

Moisture ratio is different in effervescent tablets and normal tablets. It is <0.3% and 2%, respectively. Effervescent tablets are commonly larger than normal tablets; and they may be easily broken or damaged. For the packaging, these details are very important to keep in mind. Dwell time should be increased to solve this problem.<sup>[3]</sup>

During filling, powder pressure is obtained by rotary valves. When lubricant is absent, the tablets can stick the walls. Lubricants may be solid or liquid.<sup>[3]</sup> During press procedure, surface materials are forced to be pressed into the tablets and moisture, absorbed from the air, is decreased.<sup>[3]</sup>

### Blister packs and tube arrangements used for packaging

Packing materials have a relatively stable shelf life. Aluminum is used instead of polymer blister materials. Because its water permeability is lower. In a package, ten or more tablets are placed. Environment should have low humidity, because humidity may destroy the tablets. Drying agents such as silica gel is incorporated into the tubes.<sup>[3]</sup>

### Advantages and Disadvantages of Effervescent Tablets

Oral forms are more preferred way of medication. In this form, slow absorption maybe the most important disadvantages. When taking the liquid form, the lower dosages can be used. Stability of active pharmaceutical ingredients is lower in liquid form. As effervescent tablets are dissolved in water just before administration, it provides advantage for the stability of these medications.<sup>[9]</sup>

Taking big tablets of capsules is difficult for the patients. Effervescent technology provides an alternative to them. Dissolving and break-down of standard tablets also takes additional time in the stomach. In effervescent, ingredients are distributed in the solution and they are not localized in certain point.<sup>[9]</sup> They can be taken in liquids and promotes patients to take more liquid. Absorption is improved and usage is easy in effervescent tablets.<sup>[9]</sup>

**Advantages of effervescent tablets:**<sup>[3]</sup> Improved taste, faster absorption, presentable fizzy tablets.

**Disadvantages of effervescent tablets:** Larger tablets, complex production process, delicate packaging process.

**Fundamentals of effervescent:** There are organic acid and alkali metal carbonate salts.<sup>[3]</sup>

### Why Effervescent Tablets Are Used?

The doses can be taken easily. The ingredients (carbonate and acid) serve as buffer for the stomach with optimum pH. The absorption occurs at 15 min.<sup>[24]</sup> Effervescent tablets are uncoated tablets.<sup>[6,25,26]</sup> They are susceptible to the stomach.<sup>[25,27]</sup> They may be taken in liquid form. If patients have swallowing difficulty, they can take these medications easily. It is well-tolerated in the stomach. After effervescent reaction, CO<sub>2</sub> is produced and it increases the penetration of active substances into the paracellular spaces.<sup>[28,29]</sup>

Lubricants are used to prevent adhesion of the tablets. Sucrose is added as hygroscopic material and cause to increase the tablet bulk. Aspartame and sucralose are the other sweeteners.<sup>[1,30]</sup> Aspirin is the most commonly used effervescent tablet.<sup>[6,31]</sup>

Effervescent tablets are used for:

- **Rapid and enhanced absorption:** It is dissolved in liquid and the ingredients are absorbed quickly. Conventional tablets are dissolved slowly and absorption is reduced.<sup>[24]</sup>
- **Optimal compatibility:** The effervescent tablet contains a balanced ratio of acids and carbonates forming a buffer. It has optimal compatibility with the stomach.<sup>[24]</sup>
- **Increase in liquid intake:** Effervescent tablets provide both the medicinal value intended and additional liquid intake. In diarrhea and high temperature in summer, intake of effervescent table with water contributes to daily liquid intake.<sup>[24]</sup>
- **Advantages in case of swallowing problems:** Effervescent tablets present an alternative for these patients.<sup>[24]</sup>
- **Simple handling and measuring into exact doses:** Effervescent tablets are dissolved quickly and the patients can obtain exact doses.<sup>[24]</sup>

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# Tracheal rupture caused by fall from a height

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## Abstract

Follow-up and treatment of multiple lesions in intensive care units are arranged within the discipline of approach to a case of injury. Herein, we present a 38-year-old female patient who had head trauma caused by a fall from a minibüs. The patient was presented to our intensive care unit with epidural hematoma; however, tracheal rupture was found during the follow-up. Tracheal injuries and especially ruptures are not frequently encountered events even in cases with severe traumas. In traumatic events, it is difficult to diagnose tracheal rupture because of serious problems related with many organ systems. After establishment of diagnosis, it is possible to encounter relevant neurological and infectious problems because of longer treatment process. As in the case with our patient, in patients without any additional previously experienced respiratory problems while intubated development of respiratory distress hours after recurrent periods of intubation and extubation should suggest the presence of tracheal rupture.

**Keywords:** Tracheal rupture, fall from a height, injury.

## Özet: Yüksekten düşmenin neden olduğu trakea rüptürü

Yoğun bakım ünitelerinde birden fazla lezyonun izlem ve tedavisi, bir yaralanma olgusuna yaklaşım disiplini kapsamında düzenlenir. Bu yazıda, bir minibüsten düşüşün neden olduğu kafa travmasına maruz kalmış 38 yaşındaki bir kadın hastayı sunduk. Hasta yoğun bakım ünitemize epidural hematomla gelmesine karşın, izlem sırasında trakea rüptürü saptanmıştır. Trakea yaralanmaları ve özellikle rüptürlere ağır travmalarda bile sıklıkla rastlanmamaktadır. Travmatik olaylarda, birçok organ sistemiyle ilgili ciddi sorunlar nedeniyle trakea rüptürüne tanı koymak zordur. Tanı konduktan sonra daha uzun tedavi süreciyle ilgili nörolojik ve enfeksiyon sorunlarına rastlamak mümkündür. Hastamızda olduğu gibi entübe iken ilave solunumsal sorunlar yaşamayan hastalarda yinelenen entübasyon ve ekstübasyon dönemlerinden saatler sonra solunum sıkıntısının gelişmesi trakea rüptürünün varlığını düşündürmelidir.

**Anahtar sözcükler:** Trakea rüptürü, yüksekten düşüş, yaralanma.

We encounter multiple cranial, thoracic, abdominal, and extremity lesions caused by traffic accidents and fall from a height. Follow-up and treatment of these cases in intensive care units (ICUs) are arranged within the discipline of approach to a case of injury. In the present case, we are dealing with a 38-year-old female patient who had head trauma caused by a fall from a minibüs. The patient was presented to our ICU with tracheal rupture.

## Case Report

A 38-year-old female patient who had an extravehicular traffic accident was sent to an external medical center and then her cerebral computed tomography (CT) was obtained because of head trauma. The patient with normal tomographic findings was admitted to ICU. When she was

admitted in ICU her consciousness was open; however, she was somnolent. She was consulted to neurosurgery department, which suggested her follow-up with cervical and cerebral CTs. She was spontaneously breathing through her intact respiratory tract and received oxygen ventilation at a rate of 3 L/min. Later on, she suffered from respiratory distress and underwent noninvasive intermittent mechanical positive pressure ventilation (NIMV). Control CT revealed right parieto-occipital epidural hematoma and then intracranial pressure catheter was implanted for drainage of the epidural hematoma. On the 9th day of her ICU stay when she was cooperative with improved general health state and open consciousness, she was transferred from ICU to the service of neurosurgery. During her transfer to the service, she had intermittent fits of coughing which we thought to be related to airway irritation during her transfer to the service.

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One day after her transfer to the service, she was readmitted to our ICU because of high fever and respiratory distress. Due to increase in the severity of respiratory distress and decrease in SPO<sub>2</sub> concentration, orotracheal intubation (OTI) was performed. Then she was connected to mechanical ventilation device and started to be sedatized. Cranial CT and thorax CT were performed to exclude cranial and thoracic pathologies. The patient was consulted to the department of infectious diseases; however, any pathology was not detected. Since she had sufficient respiratory exertion with normal blood gas parameters while intubated, her OTI was terminated. However, because of development of respiratory failure one day later she was re-intubated. ENT consultation requested for the evaluation of vocal chords could not detect any abnormal finding and endoscopy was recommended for the patient. Meanwhile, hematemesis developed and endoscopy performed during requested gastroenterology consultation did not reveal any important abnormality. The patient, whose respiratory functions were satisfactory while on OTI, was re-extubated. Following extubation, NIMV was applied intermittently at PS mode. Our patient tolerated NIMV for nearly 4–5 days. However, because of persistence of her respiratory distress and requirement for continuous NIMV, she underwent OTI again. Because of inadequate swallowing reflex and frequent trials of intubation–extubation, percutaneous endoscopic gastrostomy and tracheostomy were planned. *Staphylococcus aureus* was grown on the culture media of her tracheal aspirate and at cardiology consultation requested for infective endocarditis any abnormality was not detected. The patient was started on linesolide and ampicillin-sulbactam therapy. Following trial of percutaneous tracheostomy performed on the 25th day of her hospitalization, the patient suffered from respiratory problems and the air delivered leaked out through mouth which necessitated re-intubation. Bronchoscopic evaluation could not identify effaced tracheal rings and cryothyroidal membrane of the patient. Tracheal region was inflamed and edematous. Tracheostomy of the patient was closed and OTI was repeated. Consultation from the Department of Otorhinolaryngology (ENT) was requested and open surgery was planned for tracheostomy. One day later, surgical tracheostomy was performed by ENT department in the operating room. However, her ventilation was still problematic and her examination revealed nearly a 3 cm long tear on the anterior aspect of the trachea. The tear was sutured. Tracheostomy incision opened by the surgery team was also sutured and closed. OTI was performed and the patient was hospitalized in the ICU. Based on the decision of the consultation council, stent implantation was planned with the aid of the bronchoscopy for the management of the tracheal rupture.

The patient was brought into the operating room by the Departments of ENT and Thoracic Surgery and tracheal avulsion was seen on the presumably ruptured tracheal region. Primary repair with end-to-end anastomosis was performed and chin was sutured to the chest wall so as to place the neck in flexion. Orotracheally intubated patient was hospitalized in ICU. During this monitorization process, the patient was sedatized and curarized (infusion therapy with midazolam 3 mg/h and vecuronium chloride 2 mg/h). On the 35th day of her hospitalization *Acinetobacter baumannii* was grown on her blood culture media. Colimycin, B-lactam and meropenem therapy was initiated. On the 40th day of her hospitalization, a posttraumatic pocket hematoma extending from sacral region to the left gluteal region was detected. The wound was debrided by plastic surgeon and VAC (vacuum assisted closure) was performed. During weaning process, she could not move her painful extremities, which suggested the presence of critical illness neuro/myopathy. She underwent electromyography (EMG) in the department of neurology and diagnosis of Gullian-Barré syndrome (AMAN form) was established. For 5 days, intravenous immunoglobulin treatment was applied and physical therapy was initiated. Fifteen days after the last operation (on the 55th day of her hospitalization), tracheostomy was opened by ENT department. Nearly one month after establishment of the diagnosis of neuropathy, she started to move her hands and arms; however, neuropathy of extremities persisted. Control thoracic and lumbar MR could not detect any abnormality responsible for the existing condition. EMG results were thought to be consistent with ICU polyneuropathy. The patient with tracheostomy was monitored under room air conditions. She was transferred to the service with open conscious, full cooperation and stable vital signs at 3rd month of her hospitalization. Myositis ossificans developed in her right leg and she received physical therapy for nearly 2 months in the service before her discharge. The patient was followed up for approximately 4 months at home; then, her tracheostomy was closed. The patient underwent a reoperation for the repair of her tracheal rupture in another center, while she was receiving physical therapy and rehabilitation and maintaining her daily life with minimal support. The patient died nearly 6 months after her discharge from our hospital because of postoperatively developed sepsis.

## Discussion

In their retrospective series of 23 patients, Hwang et al. could not detect any significant difference between prognoses of patients diagnosed within or 48 hours after penetrating and blunt injuries. Since patients who applied to the



emergency services were mostly polytraumatic cases, the authors revealed difficulties in making a diagnosis. In addition, they attributed cause of death of the patients who were brought to the emergency services to possibly overlooked diagnosis of tracheal rupture.<sup>[1]</sup> We also could hardly diagnose tracheal rupture of our patient. However, in a case presented by Gorosh et al., the authors described diagnostic difficulties and treatment of spontaneous tracheal rupture in a 3-year-old baby boy who had been brought to the emergency service with the initial diagnosis of anaphylaxis and rapidly deteriorated with progressive edema and respiratory distress. Bronchoscopy could not demonstrate the preexisting pathology. On computed tomograms, a defect extending proximally along the posterior wall of the trachea up to the end point of the endotracheal tube was detected. In conclusion, the authors indicated that spontaneous tracheal rupture can be overlooked and its diagnosis might be challenging.<sup>[2]</sup> We also had difficulty in making a diagnosis with the aid of computed tomography and bronchoscopy. However, during surgical procedure, tracheal avulsion could be detected. In a case presentation Austin et al. detailed airway management strategy in patients whose tracheas had been perforated during endotracheal intubation. They emphasized that the clinicians could be able to use at least more than one airway devices and be prepared to face these types of unexpected conditions.<sup>[3]</sup> In the present case, we experienced difficulties in the detection of anatomical variations of trachea. In their case report on spontaneous tracheal rupture caused by vomiting, Stevens et al. presented a 14-year-old girl with type I DM and respiratory distress who had very severe vomiting bouts for 4 days and diagnosed as diabetic ketoacidosis. Her examination revealed presence of tachypnea, subcutaneous emphysema in her neck and upper chest. Pneumomediastinum was observed on her chest X-ray. Any evidence of esophageal rupture was not encountered. On chest CTs, a rupture of 3.5 cm in length extending distally to the cricoid cartilage on the posterior aspect of the trachea had been observed. In conclusion, in this first published case of tracheal rupture secondary to vomiting, the authors indicated that in cases with subcutaneous emphysema, pneumomediastinum and similar diagnoses, esophageal and tracheal rupture should be ruled out.<sup>[4]</sup> In our case, we also ruled out this diagnosis by performing endoscopy so as

to exclude esophageal rupture or perforation which might be related to tracheostomy. In their study entitled "Surgery of traumatic tracheal and tracheobronchial injuries". Palade and Passlick indicated that these injuries had been rarely seen. It has been also indicated that successful treatments of these injuries require rapid and direct diagnostic evaluation. Despite requirement of surgical procedure in cases with posttraumatic injuries is conceived, recently conservative treatment in iatrogenic injuries outweighs all other alternatives.<sup>[5]</sup> In our case, we have observed that rare diagnosis of tracheal avulsion could be treated only with surgical method and long-term monitorization in ICU. During this process, we encountered infections which can be seen associated with long-term ICU stay. In addition, in our patient critical illness neuro/myopathy developed secondary to sedation and use of steroids and neuromuscular blockers.

Tracheal injuries and especially ruptures are not frequently encountered events even in cases with severe traumas. In traumatic events, it is difficult to diagnose tracheal rupture because of serious problems related with many organ systems. After establishment of diagnosis, it is possible to encounter relevant neurological and infectious problems because of longer treatment process. As in the case with our patient, in patients without any additional previously experienced respiratory problems while intubated development of respiratory distress hours after recurrent periods of intubation and extubation should suggest the presence of tracheal rupture.

**Conflict of Interest:** No conflicts declared.

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## **Retraction: Yurttaş V et al. Prognostic factors for graft success in tympanoplasty with mastoidectomy. ENT Updates 2015;5:72–75**

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The authors of the above article discovered a significant inaccuracy in their own paper that has been published in ENT Updates 2015;5(2):72–75. They retract this publication due to duplicate publication of the same material in another issue of the same journal by mistake.

Yukarıda başlığı bulunan ENT Updates 2015;5(2):72–75 künyeli makalenin yazarları yayımlanma sonrasında çalışmanın yanlışlıkla aynı derginin bir başka sayısında mükerrer olarak basıldığını fark ettiklerinden dolayı bu makaleyi geri çekmişlerdir.

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