# CLINICAL OUTCOMES AND ETIOLOGICAL FACTORS IN OCULAR CHEMICAL AND THERMAL BURNS

## Oküler Kimyasal ve Termal Yanıklarda Klinik Sonuçlar ve Etiyolojik Faktörler

Cisil ERKAN POTA1, Ozge Ekin GECER SERIFOGLU2, Olgar OCAL1, Hatice Deniz ILHAN1

## **ABSTRACT**

**Objective:** To evaluate the clinical findings of patients admitted to the emergency department due to thermal and chemical ocular burns and to investigate the etiological causes.

Material and Methods: Four hundred seventy-four (9.8%) chemical and thermal ocular burn cases presented to the emergency department of Akdeniz University Faculty of Medicine between 2019 and 2024 were evaluated. Patients' age, gender, exposure, initial examination findings, and post-treatment permanent damage status were evaluated.

Results: Of the 474 patients included in the study, 82.1% were adults and 17.9% were pediatric. Corneal burns were most commonly observed in the pediatric group due to adhesives, while in the adult group, bleach (sodium hypochlorite) was the most common cause of corneal burns. Bleach, adhesives, and thermal burns were observed to be the most common causes of initial examination damage, while bleach was the most common cause of permanent damage complications. Significant differences were found between the causative agents in terms of both initial examination findings and permanent complications (p<0.001, p<0.025). Bleach caused the most permanent damage. Adhesives and neutral substances were the most common causative agents in the pediatric group, while bleach and acidic substances were the most common in adults (p<0.001). Limbal ischemia was not detected in the pediatric group, and there was no difference in the complication rate between the two groups (p=0.597). Vision loss and permanent damage affecting the ocular surface were observed in 5 (1.05%) of the patients. We observed that patients may experience corneal vascularization, leukoma, symblepharon, corneal stromal scarring, and trichiasis secondary to limbal ischemia and other ocular surface problems.

**Conclusion:** In conclusion, chemical and thermal corneal burns are serious ophthalmic emergencies. It should be noted that alkali burns lead to more severe outcomes and that early treatment is associated with better prognosis. We believe early intervention and appropriate treatment are critical in promoting healing of the ocular surface and preventing permanent vision loss.

**Keywords:** Ocular Chemical Burn; Thermal Corneal Burn; Corneal Burn; Limbal İschemia; Leukoma; Symblepharon

#### ÖZET

Amaç: Acil servise termal ve kimyasal oküler yanık nedeniyle başvuran hastaların muayene bulgularının değerlendirilmesi ve etiyolojik nedenlerin araştırılması

Gereç ve Yöntemler: 2019-2024 yılları arasında Akdeniz Üniversitesi Tıp Fakültesi acil servisine başvuran

474 (%9,8) kimyasal ve termal oküler yanık olgusu olduğu değerlendirildi. Hastaların yaş, cinsiyet, maruz kaldıkları etken maddeler, ilk muayene bulguları ve tedavi sonrası kalıcı hasar durumu ve değerlendirildi. **Bulgular:** Çalışmaya dahil edilen 474 hastadan %82,1'i yetişkin, %17,9'u pediatrik yaş grubundadır. Pediatrik grupta en sık yapıştırıcı, yetişkin grupta ise çamaşır suyu (sodyum hipoklorit) nedeniyle korneal yanık gözlenmiştir İlk muayenedeki hasar açısından çamaşır suyu, yapıştırıcı ve termal hasarın en sık bulguya yol açtığı, kalıcı hasar açısından ise en sık komplikasyona çamaşır suyunun sebep olduğu gözlendi. Etken maddeler arasında hem ilk muayene bulguları hem de kalıcı komplikasyonlar açısından anlamlı fark bulunmuştur (p<0,001; p<0,025). En fazla kalıcı hasara çamaşır suyu yol açmıştır. Pediatrik grupta en sık etken yapıştırıcı ve nötr maddelerken, yetişkinlerde çamaşır suyu ve asidik maddeler ön plandadır (p<0,001). Pediatrik grupta limbal iskemi saptanmamış, iki grup arasında komplikasyon oranı açısından fark bulunmamıştır (p=0,597). Hastaların 5'inde (%1,05)'inde görme kaybı ve oküler yüzeyi etkileyen kalıcı hasar gözlenmiştir.Hastalarda limbal iskemi ve diğer oküler yüzey problemlerine sekonder olarak korneal vaskülarizasyon , lökom, semblefaron, korneal stromal skar ve trikiazis olabileceğini gözlemledik.

Sonuç: Sonuç olarak, kimyasal ve termal korneal yanıklar ciddi oftalmik acil durumlardır. Alkali yanıkların daha ciddi sonuçlar doğurduğu ve erken tedavi ile daha iyi prognozlar elde edilebileceği unutulmamalıdır. Erken müdahale ve doğru tedavi, oküler yüzeyin iyileşmesini sağlamak ve kalıcı görme kaybını engellemek için kritik öneme sahip olduğunu düşünüyoruz .

Anahtar Kelimeler: Oküler Kimyasal Yanık; Termal Korneal Yanık; Korneal Yanık; Limbal İskemi; Lökom; Semblefaronsemblefaron

<sup>1</sup>Akdeniz Üniversitesi, Tıp Fakültesi, Antalya, Türkiye. <sup>2</sup>T.C. Sağlık Bakanlığı, Erzincan Binali Yıldırım Üniversitesi, Mengücek Gazi Eğitim ve Araştırma Hastanesi, Erzincan.

Çisil ERKAN POTA, Dr.

Türkiye.

(0000-0003-2544-6618) cisilerkann@gmail.com Özge Ekin GEÇER ŞERİFOĞLU, Dr.

EÇER ŞERIFOGLU, Dr. (0000-0002-0458-5582)

ozgeekin.gecer@gmail.com Olgar ÖCAL, Dr.

(0000-0002-1842-0906) ocalolgar@gmail.com

Hatice Deniz İLHAN, Dr.

(0000-0002-5085-4763) drdenizilhan@gmail.com

#### iletisim:

Dr. Çisil ERKAN POTA Pınarbaşı Mah. Akdeniz Üniversitesi Tıp Fakültesi Hastanesi, 07070, Konyaaltı/ Antalya/Türkiye.

Geliş tarihi/Received: 24.05.2025 Kabul tarihi/Accepted: 19.07.2025 DOI: 10.16919/bozoktip.1700287

Bozok Tip Derg 2025;15(3):317-323 Bozok Med J 2025;15(3):317-323

## **INTRODUCTION**

Corneal burns are vision-threatening ophthalmic emergencies that require immediate intervention. Chemical eye injuries account for approximately 11- 22% of all eye trauma cases (1). Severe ocular complications and vision loss may develop following chemical corneal burns. Some of these complications include limbal stem cell deficiency, conjunctivalization, keratitis, conjunctivitis, neovascularization, corneal inflammation, ulceration, and symblepharon in severe burn cases (2). Early intervention is critical in determining prognosis. The duration of exposure, the concentration and pH of the causative agent, as well as the depth of injury, determine the severity of complications (3).

One of the most important causes of vision loss is limbal stem cell deficiency (LSCD). Following LSCD, a significant decrease in corneal clarity and visual acuity may occur (4, 5). Acute ocular burns are responsible for 84% of unilateral and 21–30% of bilateral limbal stem cell deficiency cases (6, 7). In addition to this, persistent epithelial defects, neovascularization, and corneal opacification secondary to limbal ischemia can lead to permanent vision loss (3).

After the removal of the causative agent from the ocular surface in the emergency setting, patients are usually managed with medical treatment. In cases where medical therapy is insufficient, surgical interventions such as amniotic membrane transplantation, conjunctival limbal autograft transplantation, conjunctival limbal allograft transplantation, or penetrating keratoplasty may be required (8).

In this study, we evaluated the etiology, prognosis, and age- and gender-based distribution of corneal burn injuries in patients who presented to the emergency department over the past five years. Final examination findings of patients who developed permanent vision loss after treatment were reviewed to assess the prognosis of burns according to etiology.

## **MATERIALS AND METHODS**

This study was approved by the local ethics committee (Approval Number TBAEK - 376) where the study was conducted, by the ethical standards of the Declaration of Helsinki. We retrospectively reviewed the data of 4821 patients who were referred to the Department

of Ophthalmology following emergency department admissions at Akdeniz University Faculty of Medicine between 2019 and 2024. A total of 474 patients diagnosed with chemical or thermal corneal burns were included in the study. Patient data including age, gender, the causative agent at the time of injury, initial examination findings, and the presence or absence of permanent damage after treatment were recorded.

According to the Roper-Hall classification, cases were staged as follows:

Stage I: Presence of corneal epithelial defect without conjunctival or corneal ischemia.

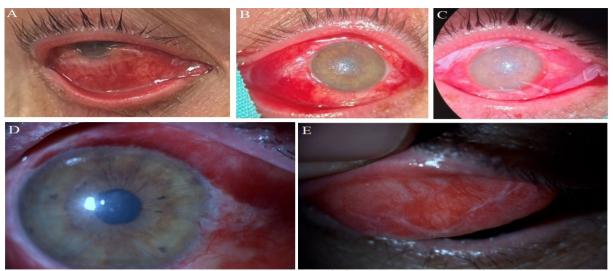
Stage II: Corneal haze with visible iris details and less than one-third limbal ischemia.

Stage III: Total epithelial loss with stromal haze obscuring iris details and one-third to one-half limbal ischemia.

Stage IV: Complete corneal opacification with obscured iris and pupil, and more than half limbal ischemia (9). During follow-up, it was observed that patients with chemical burns were first irrigated with saline in the emergency department and then referred for ophthalmologic consultation. Depending on the extent of the epithelial defect and injury severity, patients were treated with topical antibiotics, preservative-free artificial tears, autologous serum drops in selected cases, and antibiotic ointment with eye patching. Subconjunctival injections of heparin, lidocaine, and adrenaline were administered to patients with limbal ischemia. In cases with large epithelial defects, therapeutic contact lenses or amniotic membrane transplantation were used for ocular surface reconstruction (Figure 1).

## **Statistical Analysis**

The statistical analysis was carried out using IBM SPSS version 23.0 software (SPSS Inc., IL-USA). To define the sample, continuous variables were expressed as mean ± standard deviation and median (minimum-maximum), and categorical variables as numbers and percentages. The categorical results were analyzed using the chi-square test and Fisher's exact test. The results were analyzed with a 95% confidence interval, and a p-value of < 0.05 was considered statistically significant.



**Figure 1.** Patient with symblepharon between the upper half of the cornea and the lid after lime burn (A). After the lid was separated from the corneal surface, edema and epithelial defect were observed in the entire cornea (B). Surface reconstruction was performed with amniotic membrane (C). Corneal healing at the fourth month follow-up (D). Remaining scar tissue on the upper eyelid palpebra conjunctiva (E)

## **RESULTS**

In the past five years, a total of 474 patients presented to the emergency department with ocular burns, accounting for 9.8% of all ophthalmology consultations. The mean age of the patients was  $32.6 \pm 16.7$  years (range: 1-81 years). Demographic data are summarized in Table 1. Of these patients, 85 (17.9%) were in the pediatric age group, while 389 (82.1%) were adults. There were 277 male patients (58.4%) and 197 female patients (41.6%).

The most common causes of ocular burns were sodium hypochlorite (bleach), thermal injuries, and adhesives. Among the agents responsible, 169 burns (35.7%) were due to acidic substances, 263 (34.2%) were caused by alkaline substances, and 140 (29.5%) were related to neutral substances. On initial examination, chemosis was observed in 19 patients, and 28 patients (5.9%) had marked eyelid edema.

In 74 patients, the ophthalmological examination was normal. According to the Roper-Hall classification, 386 patients were classified as Stage I (8 of them had extensive epithelial defects), 9 as Stage II, 4 as Stage III, and 1 as Stage IV. Limbal ischemia was detected in 14 patients: 3 cases were caused by sodium hypochlorite (bleach), 2 by boiling water, 2 by acid, 2 by lime, 2 by caustic substances, 2 by cologne, and 1 by hot oil. At

the final examination, only 5 patients (1.05%) had permanent vision loss, and all of them were adults. These cases are summarized in Table 2. No permanent damage was detected in the remaining patients.

Patients were evaluated in terms of etiological agents. Significant differences were observed in terms of age group, gender, initial examination findings and permanent complications. We found that age and gender did not cause a significant difference in terms of permanent complications (Table 3). Adhesives most frequently caused extensive epithelial defects due to prolonged contact with the cornea. Hot water and steam were most commonly associated with eyelid edema. Bleach, detergents, and limescale removers typically caused epithelial defects and chemosis.

There was also a statistically significant difference among agents in terms of permanent complications (p < 0.025), with bleach exposure being the most common cause of long-term damage. However, no statistically significant association was found between the chemical nature of the substance (acidic, alkaline, or neutral) and the likelihood of developing permanent complications (p = 0.245).

There was no significant difference in gender distribution between the pediatric and adult groups (p = 0.545). When causative agents were compared, a

significant difference was observed between the two age groups. In the pediatric group, adhesives were the most common cause, whereas in adults, bleach exposure was more frequent (p < 0.001). Neutral agents were more commonly responsible in pediatric patients, while acidic agents were more common in adult patients (p < 0.001).

There was a significant difference in the extent of ocular involvement at presentation between the two age groups (p = 0.004). In both groups, the most

frequent clinical finding was punctate epithelial defect; however, limbal ischemia was not observed in the pediatric group. No significant difference was found between the groups in terms of permenant complication rates (p = 0.597).

When analyzed by gender, females were more frequently injured by bleach and other household cleaning products, whereas males had a higher incidence of injuries caused by agricultural chemicals, acids, and adhesives (p < 0.001). There was no significant

Table 1. Demographic characteristics and causative agents in patients with ocular burns

	Number of patients	Percentage(%)
Age Group		
Adult	389	82.1
Pediatric	85	17.9
Gender		
Male	277	58.4
Female	197	41.6
Ph		
Acid	169	35.7
Base	263	34.2
Neutral	140	29.5
Etiological Agents		
Bleach (sodium hypochlorite)	98	20.7
Thermal	87	18.4
Glue	63	13.3
Porous (sülfamik asit)	50	10.5
Acid	30	6.3
Lime (CaO)	10	2.1
Others (acetone, cologne, pesticide,	136	28.6
caustic substance, paint )		
Examination Findings No finding	74	15.6
Roper Hall		
Stage 1	386	81.5
Stage 2	9	1.9
Stage 3	4	0.8
Stage 4	1	0.2
Examination Findings		
Epithelial damage	400	84.3
Chemosis	19	4
Eyelid edema	28	5.9
Limbal ischemia	14	2.9

Table 2. Clinical features and final outcomes of patients with permanent vision loss

Patient No	Age	Gender	Roper Hall Stage	Etiological Agent	Final VA	Complications
					(logMAR)	
1	28	Male	4	Pesticide (phosphorous acid)	1.80	Limbal ischemia, Leukoma,
						Corneal vascularization
2	38	Male	3	Bleach (sodium hypochlorite)	0.52	Corneal vascularization,
						symblepharon
3	59	Female	3	Bleach (sodium hypochlorite)	1.80	Corneal stromal scarring,
						vascularization
4	36	Male	3	Paint ( Titanium dioxide?)	1.80	Leukoma
5	66	Male	3	Caustic substance (sodium hidroksit	0.22	Symblepharon

Table 3. Comparison of patient data according to etiological agent and permanent complication

	Etiological Agent	Permanent Complication	
	(p value)	(p value)	
Pediatric/Adult	< 0.001*	0.597*	
Male/Female	< 0.001*	0.408*	
Finding at initial examination	< 0.001*	< 0.001*	
Permanant Complication	0.025*	-	

<sup>\*</sup> Chi square test

difference between males and females in terms of corneal involvement (p = 0.790) or complication rates (p = 0.408).

## **DISCUSSION**

In this study, the number of male patients with chemical and thermal corneal burns was higher than the number of female patients, and the number of adult patients was higher than that of pediatric patients. In the pediatric group, the most common cause of burns was adhesives, while in the adult group, bleach was the most common cause. Regarding the damage at the initial examination, bleach, adhesives, and thermal burns were the most frequent causes of clinical findings. In terms of permanent damage, bleach was the most common cause of complications. We believe that early presentation to the emergency department and prompt treatment of the ocular surface following chemical exposure are critical for prognosis.

Alkaline injuries are frequently encountered in industrial accidents due to their widespread use (10). After alkaline exposure, saponification can occur in the cell membranes due to their lipophilic nature, and

penetration can occur more rapidly compared to acids, leading to more severe damage. Vascular damage may occur, resulting in ischemia. In contrast, acid injuries cause coagulation, which limits penetration (11). In another study, 80.9% of chemical injuries were due to alkaline exposure, and 48% of alkaline injuries were classified as severe (8). In our study, half of the chemicals that caused limbal ischemia were alkaline. Among the 14 patients with limbal ischemia, 5 experienced a decrease in visual acuity.

A significant portion of ophthalmology consultations in the emergency department is composed of ocular burns. In a previous study, 0.1-15.5% of hospitalized ocular trauma cases were due to chemical ocular injuries, and this rate has increased over time (12, 13). Another study reported that in 2008, 15.5% of hospitalized acute ocular injuries were due to chemical ocular damage (14). Previous studies conducted in Turkey have reported that 11%-13% of emergency ocular trauma cases were due to chemical ocular damage (15, 16). In our study, 9.8% of patients who presented to the emergency department had chemical and thermal burns. Given the necessity for early

intervention, prompt presentation to the emergency department after an injury is crucial for a favorable visual prognosis and ocular surface rehabilitation.

In most studies, the percentage of mild injuries ranged between 57%-70% (17). Another study in the United Kingdom found that 83% of cases were low-grade injuries (18). In our study, 83.7% of patients had mild injuries.

With the COVID-19 pandemic and the widespread use of disinfectants, the number of injuries caused by hand sanitizers has started to increase. Particularly, it has been found that the number of injuries in the pediatric age group has doubled during the pandemic compared to 2019. It has been noted that alcoholbased disinfectants have become more common (17, 19).

In a previous study, it was found that roughly two-thirds of chemical eye injuries affect young males (17, 20). In our study, 55% of patients were male. However, injuries caused by domestic products were more common in females. In terms of age, it was found that 19.9% of patients presenting to the emergency department with chemical ocular trauma in the United States were children (21). Similarly, in our study, 17.9% were in the pediatric age group. Previous studies have also indicated that the ratio of acid/alkali/neutral agents in pediatric patients is different from that in adults. One study mentioned that acid-related injuries were more common than alkaline injuries (21). In another study, it was found that 51.6% of the injuries in children were caused by neutral or unknown agents. Our study also found that the most common cause of injury was exposure to a neutral agent, which accounted for 52.9%. In another study, it was determined that 27% of the pediatric injuries were in children aged 5 years and under, with a mean age of  $10.4 \pm 5.5$  years (22). In our study, 30% of the pediatric patients were in the 1-2 years age group, and 40% were under 5 years old. The mean age of the pediatric group was  $9 \pm 6.3$  years. After chemical corneal burns, cases in stages I- II typically respond to medical treatment. Advanced cases may require surface reconstruction (8). In addition to standard medical treatment, autologous serum can be used to support epithelialization. The epidermal growth factor, lactoferrin, and lysozyme in autologous serum can accelerate epithelialization (8). Additionally,

amniotic membrane transplantation can be used to protect the ocular surface and reduce inflammation (23). If these treatments are insufficient, conjunctival limbal autograft transplantation, conjunctival limbal allograft transplantation, keratolimbal allograft transplantation, or penetrating keratoplasty may be required (24). Close follow-up is crucial to guide patients toward appropriate treatment.

There are some limitations in this study. The first limitation is the retrospective analysis of the data. The second limitation is that, due to corneal opacity and vascularization, surgeries such as penetrating keratoplasty or other additional surgeries have not yet been performed for some patients, meaning the long-term follow-up results are unknown. Additional studies are needed to evaluate the long-term follow-up outcomes of these patients.

#### CONCLUSION

In conclusion, ocular injuries are among the most serious ocular emergencies. It is important to recognize that alkali burns can cause more severe damage, and due to their widespread use in industry, taking preventive measures against occupational accidents is crucial. Additionally, in the pediatric age group, treatment approaches should consider that the etiology and prognosis differ from those in adults. To prevent vision loss and ensure stabilization and healing of the ocular surface, it is important to apply correct and rapid treatment in the early period and intervene in complications at an early stage.

## Acknowledgment

The authors declare that they have no conflict of interest to disclose

## **REFERENCES**

- 1. Clare G, Suleman H, Bunce C, Dua H. Amniotic membrane transplantation for acute ocular burns. Cochrane Database Syst Rev. 2012;2012(9):CD009379
- **2.** Sharma N, Kaur M, Agarwal T, Sangwan VS, Vajpayee RB. Treatment of acute ocular chemical burns. Surv Ophthalmol. 2018;63(2):214-35.
- **3.** Tuft SJ, Shortt AJ. Surgical rehabilitation following severe ocular burns. Eye (Lond.) 2009;23:1966-71.
- **4.** Kate A, Basu S. A review of the diagnosis and treatment of limbal stem cell deficiency. Front Med. 2022;25;9:836009.

- **5.** Deng SX, Borderie V, Chan CC, Dana R, Figueiredo FC, Gomes JAP et al. Global consensus on the definition, classification, diagnosis and staging of limbal stem cell deficiency. Cornea. 2019;38(3):364–75.
- **6.** Vazirani J, Nair D, Shanbhag S, Wurity S, Ranjan A, Sangwan V. Limbal stem cell deficiency-demography and underlying causes. Am J Ophthalmol. 2018;188:99–103.
- **7.** Cheung AY, Sarnicola E, Denny MR, Sepsakos L, Auteri NJ, Holland EJ. Limbal stem cell deficiency: demographics and clinical characteristics of a large retrospective series at a single tertiary referral center. Cornea. 2021;40(12):1525–31.
- **8.** Kılıç Müftüoğlu İ, Aydın Akova Y, Çetinkaya A. Clinical Spectrum and Treatment Approaches in Corneal Burns. Turk J Ophthalmol. 2015;45(5):182–7.
- **9.** Roper-Hall MJ. Thermal and chemical burns. Trans Ophthalmol Soc UK. 1965;85:631-53.
- **10.** Welling JD, Pike EC, Mauger TF. Alkali Burn of the Ocular Surface Associated With a Commonly Used Antifog Agent for Eyewear: Two Cases and a Review of Previous Reports. Cornea. 2016;35(2):289–91.
- **11.** Morgan SJ. Chemical burns of the eye: causes and management. Br J Ophthalmol. 1987;71(11):854–57
- **12.** Koh DH, Lee SG, Kim HC. Incidence and characteristics of chemical burns. Burns. 2017;43(3):654–64
- **13.** Li T, Jiang B, Zhou X. Clinical characteristics of patients hospitalized for ocular chemical injuries in Shanghai from 2012 to 2017. Int Ophthalmol. 2020;40(4):909–16.
- **14.** Radosavljević A, Kalezić T, Golubović S. The frequency of chemical injuries of the eye in a tertiary referral centre. Srp Arh Celok Lek. 2013;141(9-10):592–6.
- **15.** Oner A, Kekec Z, Karakucuk S, Ikizceli I, Sözüer EM. Ocular trauma in Turkey: a 2-year prospective study. Adv Ther. 2006;23(2):274–83.
- **16.** Milton R, Mathieu L, Hall AH, Maibach HI. Chemical assault and skin/eye burns: two representative cases, report from the Acid Survivors Foundation, and literature review. Burns. 2010;36(6):924–32.
- **17.** Akgun Z, Selver OB. Epidemiology and etiology of chemical ocular injury: A brief review. World J Clin Cases. 2023;11(6):1245-51.
- **18.** Kuckelkorn R, Kottek A, Reim M. Intraocular complications after severe chemical burns--incidence and surgical treatment. Klin Monbl Augenheilkd. 1994;205(2):86–92.
- **19.** Wasser LM, Koppel JH, Zadok D, Berkowitz L, Abulafia A, Heiman E. et al. Pediatric Ocular Injury Due to Hand Sanitizer Exposure: An Emerging Hazard. Pediatr Emerg Care. 2021;37(9):462–5.
- **20.** Islam SS, Nambiar AM, Doyle EJ, Velilla AM, Biswas RS, Ducatman AM. Epidemiology of work-related burn injuries: experience of a state-managed workers' compensation system. J Trauma. 2000;49(6):1045–51.

- **21.** Haring RS, Sheffield ID, Channa R, Canner JK, Schneider EB. Epidemiologic Trends of Chemical Ocular Burns in the United States. JAMA Ophthalmol. 2016;134(10):1119–24.
- **22.** Korkmaz I, Palamar M, Egrilmez S, Yagci A, Barut Selver O. Ten Years of Pediatric Ocular Chemical Burn Experience in a Tertiary Eye Care Center in Turkey. Eye Contact Lens. 2022;48(4):175–9.
- **23.** Çakır H, Utine CA. Konjonktiva hastalıklarında cerrahi yöntemler-II;konjonktival flep, muköz membran grefti, amniyotik membran transplantasyonu. Turkiye Klinikleri J Ophthalmol. 2008;1(3):147-54.
- **24.** Chan CC, Biber JM, Holland EJ. The modified Cincinnati procedure:combined conjunctival limbal autografts and keratolimbal allografts for severe unilateral ocular surface failure. Cornea. 2012;31(11):1264-72.