

Journal of the Hellenic Veterinary Medical Society

Vol 74, No 2 (2023)



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doi: [10.12681/jhvms.28242](https://doi.org/10.12681/jhvms.28242)

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To cite this article:

Demir, A., & Sensoy, S. (2023). Corneal Diseases in Cats: A Retrospective Study of 477 Cases (2015-2020) . *Journal of the Hellenic Veterinary Medical Society*, 74(2), 5583–5598. <https://doi.org/10.12681/jhvms.28242> (Original work published July 4, 2023)

Corneal Diseases in Cats: A Retrospective Study of 477 Cases (2015-2020)

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ABSTRACT: Corneal diseases are common in cats. If not diagnosed and treated in time, they can cause vision loss or even eye loss. This retrospective study aimed to introduce corneal disorders in cats, briefly explaining the therapeutic management of these disorders, and exploring the possibility of breed, age, and sex predisposition. In the study, a total of 477 cats, referred to the clinics of Istanbul University-Cerrahpaşa, Faculty of Veterinary Medicine, and Department of Surgery between 2015-2020 with ophthalmological complaints and diagnosed with and treated for corneal disorders, were retrospectively evaluated. The most commonly encountered corneal disease was corneal ulcers (n=208, 43.60%), followed in descending order by corneal sequestrum (n=71, 14.8%), and corneal opacities (n=57, 11.9%) due to infection-associated symblepharon. Overall prevalence rates of ulcerative keratitis and non-ulcerative keratitis were 59.6% and 35.9%, respectively, in the study's entire cat population. The congenital corneal diseases, such as persistent pupillary membrane (PPM) and corneal opacity due to endothelial dystrophy and acquired corneal disorders, such as corneal degeneration, scarring, and endothelial degeneration, were less frequently monitored conditions. In this study, it was seen that some corneal diseases in cats are more common in cats of certain breeds and ages, and corneal diseases are diseases that can be treated with early diagnosis. It has been noted that certain diseases are of infectious origin and are more likely to be treatable conditions.

Keywords: cat, cornea, corneal ulcer, keratitis, prevalence, sequestrum.

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Date of initial submission: 13-10-2021
Date of acceptance: 23-12-2022

INTRODUCTION

Corneal diseases are frequently encountered in small animal clinical practice. Unless timely diagnosed and precisely treated, they are one of the leading causes of low vision and even blindness (Moore, 2005; Barachetti, 2010; Balland et al., 2016). The corneal lesions may emerge either as a primary entity or indicate an underlying intraocular disorder and systemic disease (Moore, 2005). Corneal diseases can be classified as congenital hereditary impairments and acquired disorders (Moore, 2005).

Early diagnosis and therapeutic approach are essential to avoid the loss in corneal transparency and thus partial vision loss and blindness. Medical and surgical treatments, individually or as a combined medical and surgical therapeutic strategy, provide quite a favorable outcome in the management of corneal disorders in cats. Medical treatments mainly comprise the topical administration of the pharmaceutical agent directly onto the defected area, while the surgical approach, which enables rapid initiation of the healing process by providing structural support to the cornea, includes partial keratectomy, keratotomy, transposition, primary closure for small-sized corneal ulcers and perforations, and transplantation (Barachetti et al., 2010; Balland et al., 2016).

The presented study aimed to introduce corneal disorders in cats, investigating the likelihood of breed, age, and gender predisposition by concisely describing therapeutic management of these disorders.

MATERIALS AND METHODS

Animals

A retrospective research, revealing the incidence and prevalence rates of different types of corneal disorders, along with descriptive evaluation of the disorder category-wise therapeutic approaches, was performed with a total of 477 cats of different breeds, ages, and gender that were submitted to the surgery clinics of the Istanbul University-Cerrahpasa, Faculty of Veterinary Medicine between January 2015 and December 2020 due to miscellaneous ophthalmological complaints.

Methods

During the ophthalmological inspections of the patients, the eye was thoroughly examined along with its entire adnexal components. Eye reflex tests (menace response, pupillary light reflex, palpebral reflex, and dazzle reflex), slit-lamp biomicroscopy, Schirmer

tear test, fluorescein stain test, tonometry, and indirect ophthalmoscopy were performed to detect corneal diseases and other comorbid potential ocular disorders. Possible surface epithelial damage of the cornea was examined by lateral illumination. The cytologic examination was carried out for the proliferative lesions. Ultrasonography (A-scan and B-scan) was required when the posterior ocular segment was invisible. Full blood count, blood biochemical analyses, and additional serological tests were also performed to detect any possible systemic diseases.

Therapeutic Approach

Medical treatment

Tiny painless corneal opacities that are not vision-threatening were left untreated. When the corneal layers were affected, the therapeutic approach (medical or surgical) was established depending on the lesion's depth. The pharmaceutical agents used for medical treatment included topical antibiotics and eye gels such as ofloxacin (Exocin, Abdi Ibrahim, 6x1 drop), cyclopentolate hydrochloride (Sikloplejin, Mefar, 2x1 drop), hyaluronic acid (Eyestil, Teka Teknik, 6x1 drop), and dexpanthenol (Recugel gel, Bausch Lomb, 3x1). Apart from topical ophthalmological drops and gels, systemic and subconjunctival drug administration was required for patients with advanced corneal disorders.

Topical tobramycin and dexamethasone suspension (Tobradex, Alcon, 4-6x1 drop) in addition to previously mentioned artificial tears were prescribed in the cases of non-ulcerative keratitis and anterior uveitis, such as corneal vascularization, granulation, pigmentation, and proliferative keratoconjunctivitis.

In the cases of local and diffuse corneal edema due to ocular conditions like glaucoma and endothelial dystrophy, antihypertensive medication containing dorzolamide hydrochloride and timolol maleate (Oftomix, Bilim, 2-3x1 drop) was combined with hyperosmolar sodium chloride solution (5% CoreDEM, 4-6x1 drop) depending on the primary underlying cause of edema.

Surgical Treatment

A partial or complete corneal debridement and lamellar keratectomy were performed using a 20G ophthalmic microsurgical knife under a surgical microscope to remove the infected and necrotic tissues or to peel the adhered corneal layer off the ocular surface to accelerate the healing process in patients with

ulcerative keratitis, keratomalacia, corneal sequestrum, and symblepharon. Nictitating membrane flap and conjunctival flaps were utilized in the surgical management of ulcerative keratitis.

Corneal perforation was repaired by simple interrupted suturing using an 8/0 absorbable suture material or conjunctival flap, depending on the extent of the lesion. The nictitating membrane flap technique was performed applying a single or two U stitches durable for 2-4 weeks in superficial and stromal ulcers, four weeks in corneal sequestrum, and 2-3 weeks in a descemetocele and conjunctival flap-related corneal perforation.

RESULTS

Study Population

Patient medical records were obtained from the Istanbul University-Cerrahpasa, Faculty of Veterinary Medicine, Animal Hospital database. Five hundred and sixty-seven eyes of 477 cats diagnosed with various ocular surface disorders were involved in the study. The distribution of corneal diseases regarding the breed, age range, affected eye, the underlying cause, and therapeutic approach were presented in Fig. 1-9 respectively. The patients aged between 2 months and 12 years, with an average of 4.1 years. Two hundred and thirty-eight cats were male (49.8%), and 239 were female (50.1%).

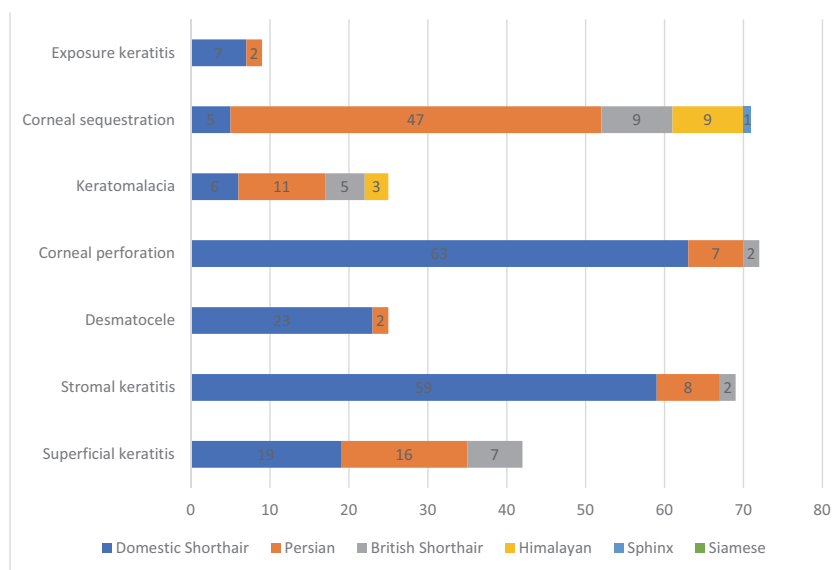


Figure 1: Distribution of diseases that cause ulcerative keratitis according to breeds

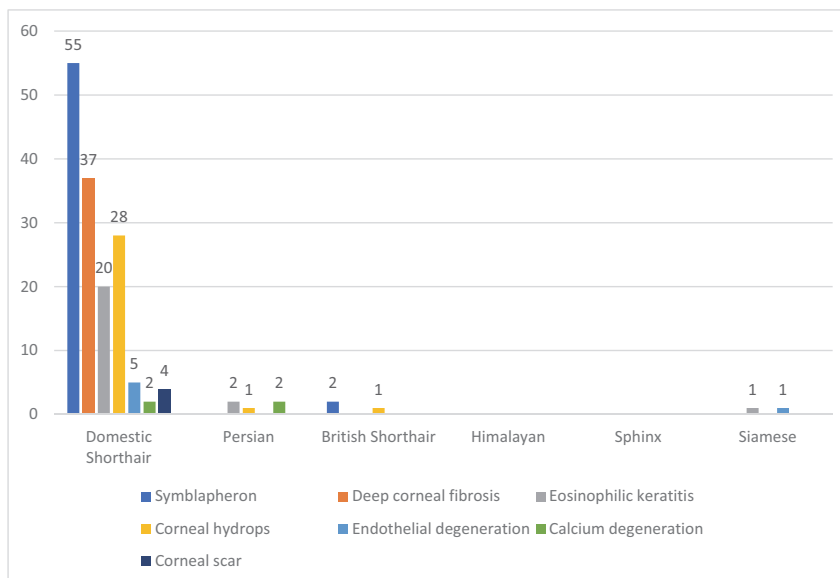


Figure 2: Distribution of diseases that cause nonulcerative keratitis according to breeds

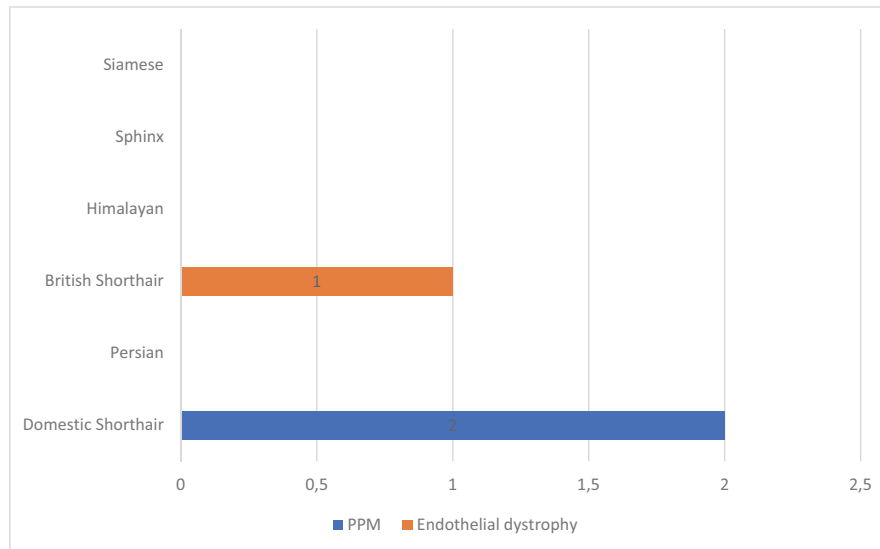


Figure 3: Distribution of congenital corneal diseases by breeds

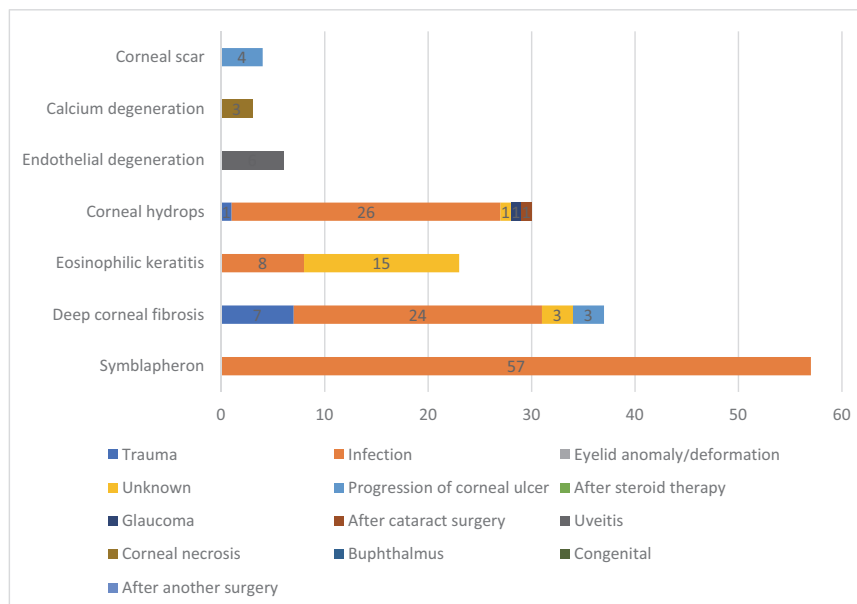


Figure 4: Etiological distribution of nonulcerative keratitis

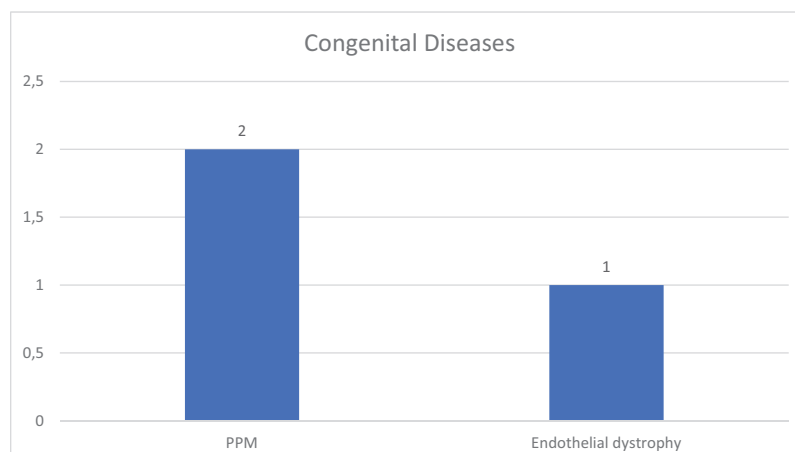


Figure 5: Etiological distribution of congenital corneal diseases

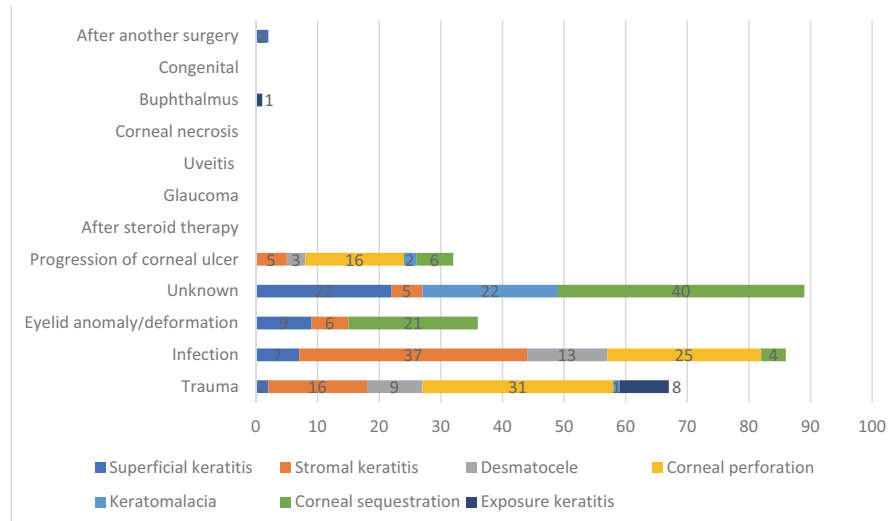


Figure 6: Etiological distribution of ulcerative keratitis

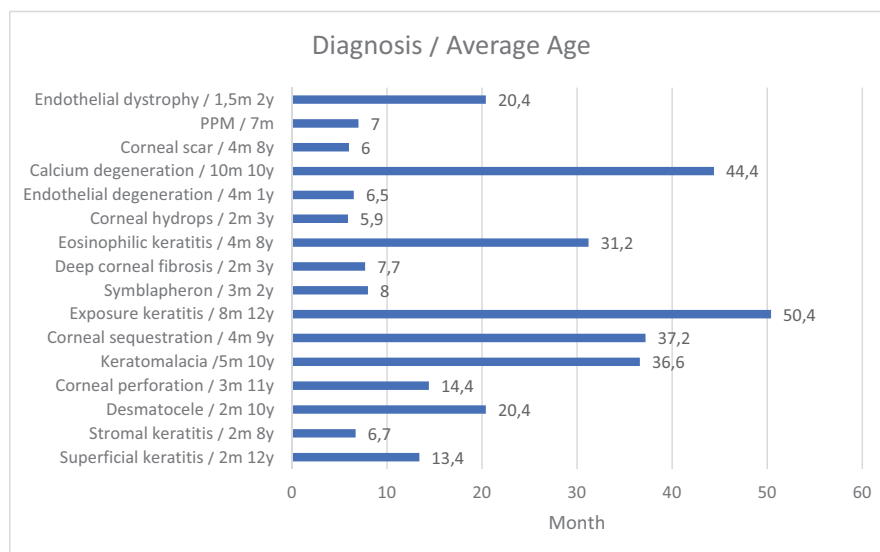


Figure 7: Distribution of corneal diseases by age

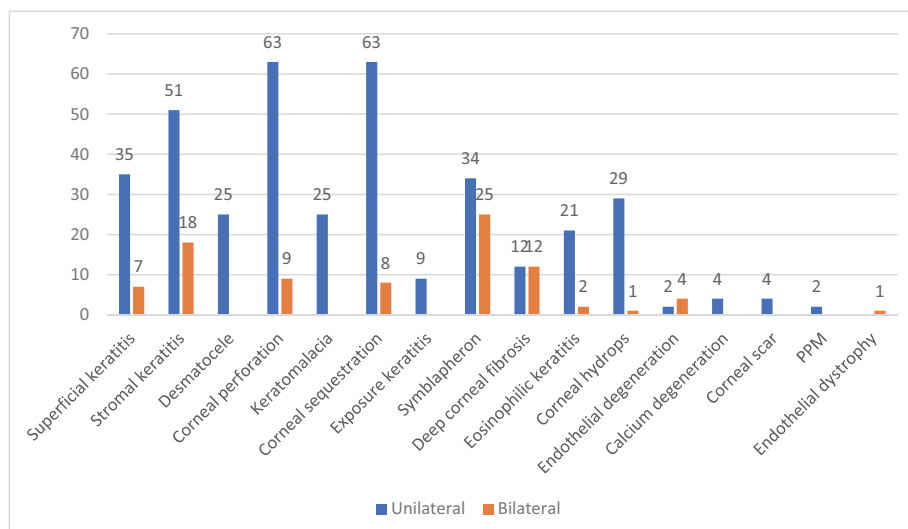


Figure 8: Corneal diseases and affected eyes

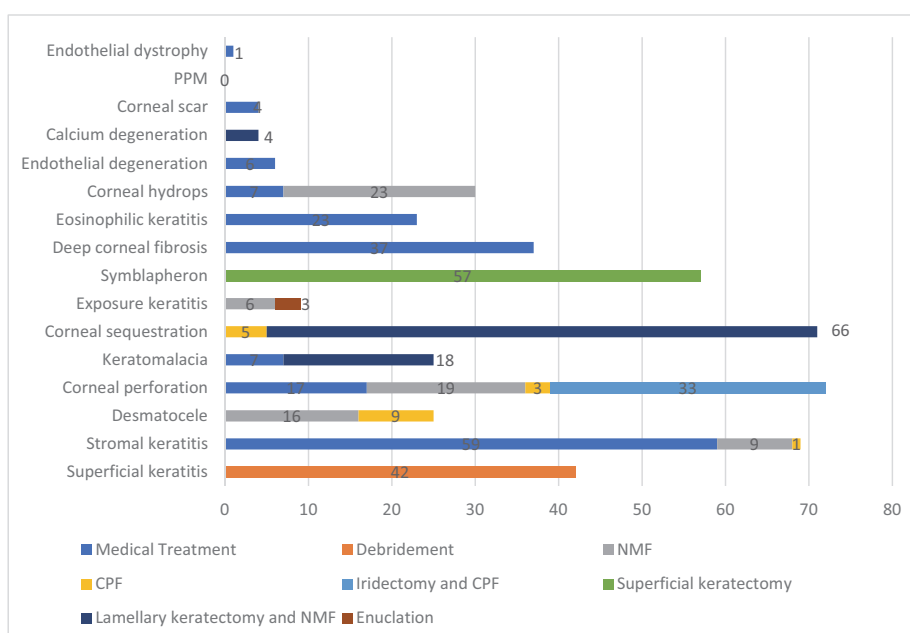


Figure 9: Medical and operative treatment methods applied to corneal diseases

Corneal Disorders

The lesions were ulcerated in 59.6%, whereas 35.9% were non-ulcerative disorders, and 0.6% comprised congenital ocular surface diseases. The diagnosed corneal diseases included superficial ulcer (8.8%) (Figure 10a), stromal ulcer (14.4%) (Figure 10b), descemetocele (5.2%) (Figure 10c) corneal perforation (15%) (Figure 10d), keratomalacia (5.2%) (Figure 11 a,b,c), corneal sequestrum (14.8%) (Figure 12 a,b,c), exposure keratitis (1.8%), corneal hydrops (6.2%), feline eosinophilic keratitis (FEK) (4.8%) (Figure 13), symblepharon-associated corneal opacity (11.9%) (Figure 14 a,b,c), deep corneal fibrosis (7.7%), endothelial degeneration of the cornea (1.2%) (Figure 15 a,b), corneal scarring (0.8%), calcareous degeneration of the cornea (0.8%) (Figure 16 a,b,c), PPM (0.4%) (Figure 17), and endothelial dystrophy (0.2%) (Figure 18).

Based on ophthalmological inspections, the most prevalent corneal diseases, in descending order, were corneal ulcers, corneal sequestrum, corneal opacities due to symblepharon, deep corneal fibrosis, corneal hydrops (Figure 19 a,b,c), keratomalacia (Figure 20 a,b), FEK in 208 (43.60%), 71 (14.8%), 57 (11.9%), 37 (7.7%), 30 (6.2%), 25 (5.2%), 23 (4.8%) cats, respectively.

Treatment protocols

In superficial lesions, after local anesthesia, debridement with a cotton swab was performed and

medical treatment was applied to all cases. Cases healed within 10-16 days and a clear image of the cornea occurred. In stromal ulcer, medical treatment in 59 cases, nictitans membrane flap after debridement in 9 cases, and conjunctival flap in 1 case. Phthisis bulbi developed in 4 of 5 cases and buphthalmos in 1, and vision could not be obtained in these eyes. Despite varying degrees of fibrosis in 12 cases, vision was achieved in 64 cases. In desmatocele cases, in addition to medical treatment, conjunctival pedicle flap was applied in 9 cases and only nictitans membrane flap was applied in 16 cases, and vision was achieved in all cases and the risk of eye loss was eliminated.

In the treatment of corneal perforations: medical treatment (17), nictitans membrane flap (19), conjunctival pedicle flap (3), iridectomy and conjunctival pedicle flap (33) (Figure 21 a,b) were applied. Vision was obtained in 7 of the cases with only medical treatment, 10 of the cases with nictitans membrane flap, 2 of the cases with conjunctival pedicle flap, and 17 of the cases with iridectomy and conjunctival pedicle flap.

After the necrotic area in the corneal sequestrum was removed by lamellar keratectomy (Figure 22 a,b,c), conjunctival flaps were applied to 5 eyes and nictitans membrane flap was applied to 74 eyes (Figure 22 d). In all cases, vision was achieved, successful results were achieved. Corneal healing was performed for 1 month in patients with nictitans membrane flap



Figure 10: Photographs showing the clinical presentation of corneal ulcers of varying depth. (a) Superficial corneal ulcer cornea stained with fluorescein dye in an 8-month-old Domestic Shorthair (DSH) cat. (b) Stromal corneal ulcer with corneal vascularization in a 14-month-old DSH cat. (c) Deep corneal ulcer with high corneal perforation in a 2-year-old DSH cat. (d) Corneal perforation and iris staphyloma in a 4-month-old DSH cat

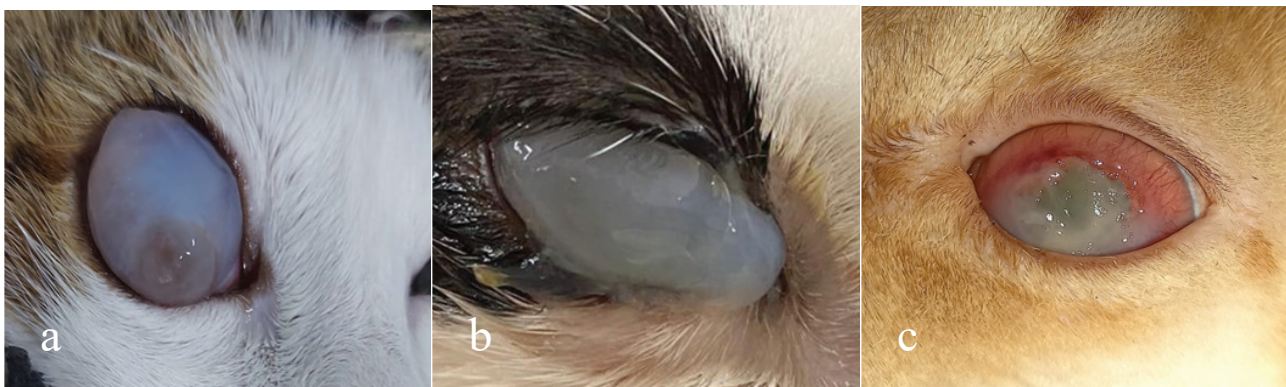


Figure 11: The appearance of infectious stromal loss and keratomalacia ("melt") in cats. a) a 6-month-old DSH, b) a 7-month-old DSH, c) a 3-year-old Persian



Figure 12: Photographs showing the clinical presentation of corneal necrosis. (a) Bilateral extensive corneal necrosis in a 5 year old Persian cat. (b) Unilateral deep corneal necrosis in a 2-year-old Persian cat. (c) Relatively extensive stromal corneal necrosis in a 3-year-old British Shorthair cat

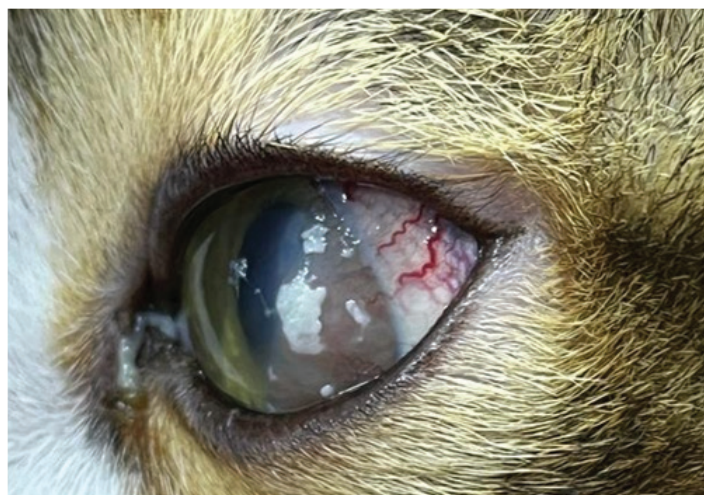


Figure 13: Eosinophilic keratitis in the left eye of an 1 year old Domestic Shorthair cat; hazy corneal opacity in the superior-temporal aspect with focal white, raised plaques



Figure 14: a) A 5-month-old DSH breed cat presented with a corneal perforation. b) Bilateral symblepharon after medical treatment. c) Appearance of corneas 1 month after superficial keratectomy



Figure 15: Due to anterior uveitis and keratic precipitates: (a) focal, ventral; (b) diffuse corneal endothelial degeneration and edema



Figure 16: Calcium microcrystal deposition on cornea. a) with corneal necrosis in a 4-year-old Persian cat, b) with corneal necrosis and superficial ulcerative keratitis in an 8-year-old Persian cat, c) after chronic corneal ulceration in a 2-year-old DSH cat



Figure 17: Persistent pupillary membrane in a 2 year old Domestic Shorthair cat



Figure 18: Bilateral corneal endothelial dystrophy in advanced stage in a 7 month old British Shorthair cat

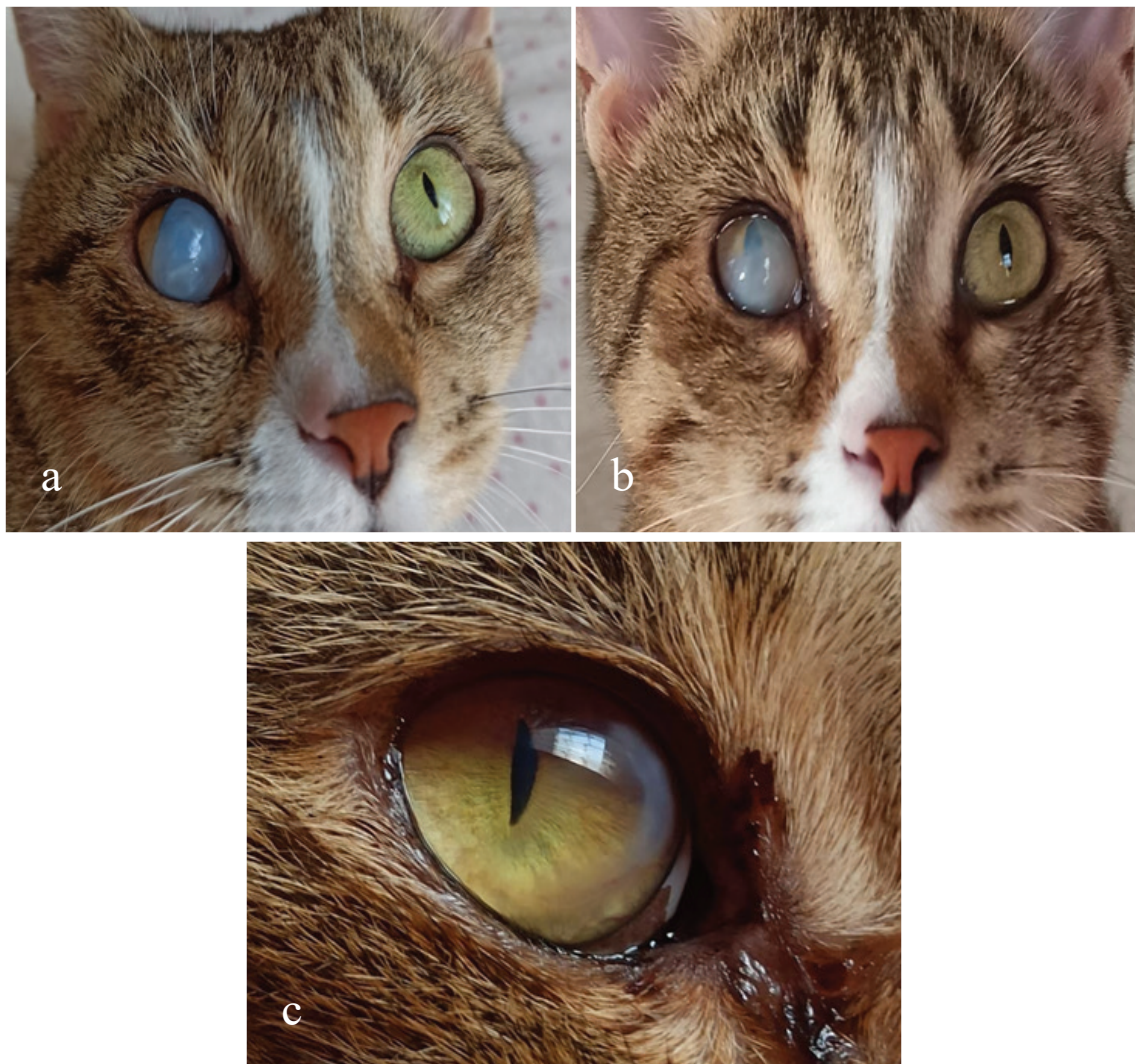


Figure 19: a) Initial appearance of unilateral acute bullous keratopathy (corneal hydrops) in a 6-year-old neutered male Domestic shorthair cat. b) Appearance of the eye at 5 days after the initial treatment. c) Appearance of the eye at 3 weeks after the treatment, focal corneal scar tissue were observed

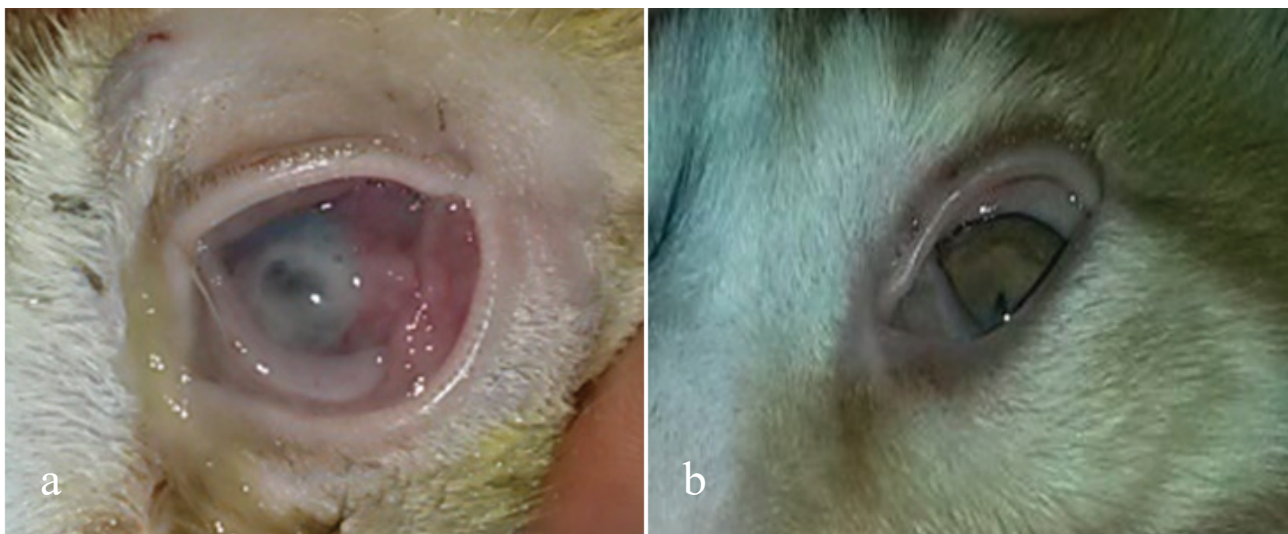


Figure 20: a) Infectious keratomalacia and severe conjunctival hyperemia in a 5-month-old DSH breed, b) 1 month after NMF technique



Figure 21: a) Post-traumatic corneal perforation and iris staphyloma in a 1 year old DSH breed cat. b) Conjunctival flap application after iridectomy in a 3-year-old DSH cat



Figure 22: a) Removal of necrotic material by lamellar keratectomy in a 2-year-old British Shorthair cat. b) The appearance of the cornea after lamellar keratectomy in 1.5 years old British Shorthair and c) 8 months old DSH breed cat. d) NMF application after lamellar keratectomy in a 2-year-old Persian cat with bilateral corneal necrosis

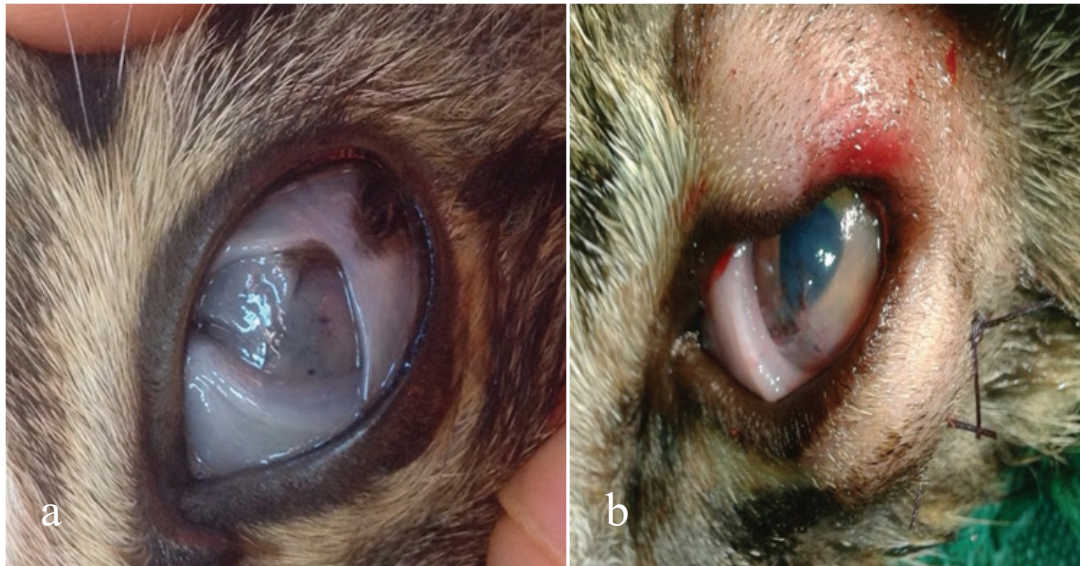


Figure 23: a) Symblepharon in a 10 month old DSH breed cat. b) The appearance of the cornea after superficial keratectomy

(NMF) and 3-4 weeks in cases with conjunctival pedicle flap (CPF). It was determined that corneal transparency lasted 5-6 weeks in NMF and 3-6 months in CPF. In the postoperative 3-year follow-up period, recurrence was observed in 4 out of 71 eyes treated with nictitans membrane flap, while none of the patients treated with conjunctival flap had a recurrence.

The symblepharon was removed by superficial keratectomy (Figure 23 a,b). Medical treatment was applied for about 4-8 weeks postoperatively. Despite medical treatment, varying degrees of corneal opacity remained in all cases. Recurrence occurred in 14 cases 3-8 weeks after the operation.

DISCUSSION

Corneal ulcers were the most prevalent ocular condition in the presented study, as were indicated in previous research (Oliver, 2003; Farghali et al., 2021), affecting 8.25% of the study's cat population, with a prevalence of 74.26% in Domestic Shorthairs and 25.73% in the brachycephalic breeds, and the average age was 12.2 months old in both breeds. The lesions were most prevalent (34.9%) in Mestizo cats, followed in descending order by British Shorthairs (16.3%) and Scottish Shorthairs (13.9%) in an age range of 1 to 5 years old. In our study, the breed-wise prevalence (Domestic Shorthairs, Persians, and British Shorthairs) was partially compatible with the previous data. Even though the brachycephalic breeds

were indicated to be more prone to develop corneal ulcers due to their exophthalmic eyeballs (Martin et al., 2019; Fargali et al., 2021), the relevant pathology is more prevalent in Domestic Shorthairs than in pure cat breeds in Turkey due to the high population of the relevant breed, mainly affecting younger individuals, unlike the previously reported data.

In the presented study, corneal ulcers developed secondary to ocular infections (39.90%) and trauma (27.40%). According to Erkan (2019) and Mezzadri et al. (2021), the primary underlying cause for corneal ulcers in cats was trauma and, less frequently, an infection. The infection-associated corneal ulcers were most frequently encountered in cats younger than 6-month-old, and trauma-associated lesions affected individuals up to 12 months old in a recent study by Farghali et al. (2021). In our study, infection-associated corneal ulcers affected the patients between 2 months and one year of age, while trauma was the leading cause in a broader age range like four months to 11 years in Domestic Shorthairs. The widespread distribution of infection-associated severe corneal lesions accompanied by an eyeball loss in young cats was considered to have developed due to low systemic and local immunity, corneal epithelial susceptibility, and reduced corneal sensitivity, enabling the rapid spread of even a simple ocular infection. Traumatic ulcerative keratitis was most prevalent in intact stray Domestic Shorthairs between 6 months and 11 years

of age, mainly due to high reproductive instinct and the constant daily struggle for food.

In a study by Kim et al. (2009) conducted with 32 dogs (36 eyes) with corneal ulcers, stromal ulcers were the most prevalent (44.44%) lesion, followed by descemetocoele (25%), superficial lesions (22.22%), and corneal perforation (9.37%) in descending order. According to Farghali et al. (2021), the most prevalent lesion was superficial corneal ulcers (43.7%), followed by stromal ulcers (12.5%). In our study, 208 cats were examined and it was shown that the most frequent lesion was corneal perforation (15%), followed in descending order by stromal (14.6%), and superficial ulcers (8.8%), and descemetocoele (5.2%).

In the presented study, corneal ulcers were treated by medical treatment and surgical interventions. In the medical therapeutic approach to corneal ulcers, Erkan (2019) had previously applied topical antibiotics, corneal collagenous enzyme inhibitor, ophthalmic anticholinergic, and artificial tears in 17 cats, while Belknap (2015) had suggested tetracycline, neomycin, polymyxin B, and bacitracin combination. We followed a protocol proposed by Kim et al. (2009) for corneal ulcers, which included topical ofloxacin combined with hyaluronic acid-containing artificial tears gel and dexpanthenol gel. A systemic antibiotic, anti-inflammatory agents, and analgesics were also prescribed, as was previously suggested for corneal perforation by Kim et al. (2009). The cats received topical antibiotics and artificial tears hourly for the first three postoperative days and then for every

2-4 h in the following days, which was a more intensive protocol even than that proposed by Erkan (2019) for corneal ulcers. Erkan (2019) medically treated 75% of their patients and preferred surgical treatment for the remaining 25%. Likewise, we applied a medical therapy for 56.2% and surgical treatment for 43.7%. Kim et al. (2009) reported that the healing process of superficial corneal ulcers treated solely with medication (44%) lasted 5.1-13.4 days, while 28.4-40 days for deep corneal ulcers treated simultaneously with medication and conjunctival flap (56%). Most superficial and stromal ulcers were successfully treated with medical therapy in 1-3 weeks in the presented study. The nictitating membrane flap and conjunctival flap were also performed when surgical intervention was considered necessary. In brief, a nictitating membrane flap was administered in 19.71% of corneal ulcers and a conjunctival flap in 6.25%. Erkan (2019) indicated that tarsorrhaphy was

performed when required in the surgical management of corneal ulcers, and the procedure revealed a favorable outcome in dogs yet failed in some cats, which afterward underwent enucleation. We administered the NMF technique in all cases of corneal ulcers, including deep ulcers such as descemetocoele, and great success was achieved with the relevant surgical technique alone combined with medication. (100% success in all 16 descemetocoele cases). No postoperative complications such as corneal perforation or severe corneal opacity due to the conjunctival flap were monitored. The vision was retrieved in 86.3% of the patients that received medical therapy and 71.4% of those that underwent surgical intervention (92.7% success for stromal ulcers and 100% for descemetocoele). Enucleation was performed in a few when the entire therapeutic approach failed, which was associated with the severity of the condition, clinical status of the affected eye, poor housing conditions, and non-adherence to medication.

In the study, corneal sequestrum was the second most common lesion (14.88%), which was compatible with the prevalence (17.95%) that was presented in the previous research by Erkan (2019) yet contradicting the findings (5%) of Ali et al. (2021). Multari et al. (2021) reported that corneal sequestrum mainly occurred in brachycephalic breeds, particularly in Persians (71.5%). Likewise, Dalla et al. (2007) showed that Persians were the most frequently affected breed (78.37%) out of 37 cats aged 12 months to 14 years old. Our study's age, breed, and gender-wise prevalences were compatible with the previous reports. Corneal sequestrum mainly occurred in purebred cats (92.95%), most commonly affecting Persians (66.19%), which supported the hypothesis of breed predilection for brachycephalic cats due to their unique anatomical conformation. The incidence increased between 2 and 5 years of age (average age=3.1 years) in the study's population aged between 4 months to 9 years old. The youngest individual was four months old with no evidence of eyelid anomaly, unlike the previously documented data, which indicated an age-wise threshold of 6 months of age (Startup 1988; Featherstone and Sansom (2004).

Laguna et al. (2015) were in favor of surgical intervention to avoid corneal sequestrum' progressing and aid the wound healing process. Galera et al. (2008) utilized lamellar keratectomy followed by the nictitating membrane flapping or conjunctival pedicle flapping, while Laguna et al. (2015) benefitted from

fresh or frozen homologous corneal graft placement. Even though the nictitating membrane flap functions as an ophthalmic bandage after the surgery, it hampers the wound site's monitoring to assess the healing process and restricts the penetration of topical drugs; therefore, it was considered contraindicated in infection-associated lesions (Startup 1988; Andrew et al., 2001). Despite its potential disadvantages, the authors suggested using this technique in the standard surgical management of corneal sequestrum, allowing immense comfort to the patient. Galera et al. (2008) achieved complete epithelial regeneration in 19.2 days by the nictitating membrane flapping and suggested an approximate follow-up period of 18.2 months. In our study, superficial ($n=6/71$) or deep partial lamellar keratectomy ($n=65/71$) was performed. After keratectomy, a nictitating membrane flap was applied solely in sixty-six cases, and additional conjunctival pedicle grafting was performed in five cases. The average recovery period was 3-4 weeks, and all patients retrieved their vision. Corneal transparency was achieved in 90.14% ($n=64/71$) with mild corneal opacity in a few patients. Recurrence was recorded in only four (5.63%) cats that underwent the nictitating membrane flapping solely during the 3-year follow-up period, which was a more favorable outcome when considering the higher recurrence rates in the previous reports by Pumphrey et al. (2019) (13%) and Featherstone and Sansom (2004) (20%). Even though there is no documented strong evidence available indicating that applying a conjunctival pedicle graft prevented the recurrence of corneal sequestrum, no recurrence was noted by this technique even after partial keratectomy, as was previously indicated by Featherstone and Sansom (2004). Furthermore, although deep and extensive defects require grafting due to potential corneal perforation, no complications were monitored by the nictitating membrane flap performed after many deep partial keratectomies, which supported the efficacy of this simple technique.

Ali et al. (2021) reported that symblepharon represented 13.75% of feline corneal diseases and ranked third among the most prevalent corneal conditions, which was compatible with our findings, with a prevalence rate of 11.94%. Dubielzig (2010) pointed to the FHV-1 infection as the underlying cause of the susceptibility for symblepharon in young cats. Likewise, Spiess (2019) emphasized the high prevalence of symblepharon in kittens due to primary exposure to the herpes virus, which rarely affects adults. According to Ali et al. (2021), the highest incidence was

noted in Domestic Shorthairs (54.54%), followed by Persians. Kim et al. (2021) encountered the lesion in a 7-month-old Persian cat. In our study, symblepharon mainly affected Domestic Shorthair cats (96.49%) and occurred in two British Shorthairs, unlike previous reports, secondary to infection. Çakmakçı (2019) pointed out the recurring role of severe primary infections causing epithelial necrosis like FHV-1 in pediatric cats. We detected symblepharon in 57 animals aged between 3 months and two years old (Average age=8 months), associated with the primary herpes virus infection in young cats based on patient history and clinical inspections. Çakmakçı (2019) showed dense adhesions between corneal and bulbar conjunctiva in the entire 28 mixed bred cats with symblepharon, and debridements performed on surgically treated cases failed to prevent multiple recurrences. Love (1975) and Kahn and Gillespie (1971) documented that surgical removal of defected tissue in partial adhesions maintained functional visual capacity; however, the condition recurred frequently in dense adhesions. In the presented study, symblepharon was treated by superficial keratectomy to remove the adhesions between the corneal and conjunctival tissues, combined with medical therapy, including topical corticosteroids. However, corneal transparency was not achieved even though the vision was retrieved. Moreover, recurrence was monitored in 24.56% ($n=14/57$) of the cases 3-8 weeks after surgery.

CONCLUSION

Based on clinical data collected from the primary care patient database, the presented retrospective study offered comprehensive information on corneal diseases and their therapeutic protocols in cats. General clinical inspections combined with patient history and complete ophthalmologic examinations revealed a high prevalence of corneal conditions in this species, as previously documented. Elaborative clinical monitoring enabled early diagnosis of ocular conditions, which could otherwise have mistakenly been neglected, and patient susceptibility, age, gender, and age distributions, the underlying causes were thoroughly investigated to determine the most efficient treatment options, which revealed favorable outcomes. We deduced that the collected data would provide complete understanding and insight concerning the potential etiology, clinical manifestations, and therapeutic approach of corneal lesions and diseases to veterinary physicians dedicated to the feline practice and also researchers in this area of expertise,

facilitating the development of novel managing approach for corneal diseases and strategies to prevent vision loss that could jeopardize the welfare and survival of the animals.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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