

Incidence and Risk Factors of New Onset Endotheliitis After Cataract Surgery

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PURPOSE. The purpose of this study was to report the characteristics of new-onset endotheliitis after cataract surgery and to identify contributing risk factors.

METHODS. In this single-center study, we retrospectively reviewed the clinical records of all patients who underwent uneventful cataract surgery in the Eye Hospital of Wenzhou Medical University between January 2015 and December 2016. Postoperative endotheliitis cases were identified by screening of keywords and individually verified by a cornea specialist. Endotheliitis rates and 95% confidence intervals (CI) were calculated. Cox proportional hazard regression analysis was used to investigate the association between endotheliitis and associated factors.

RESULTS. A total of 20,743 cataract surgeries were performed. Fifty-nine eyes developed endotheliitis after cataract surgery, with an incidence of 0.28%. The mean interval between surgery and first record of endotheliitis was 24.51 ± 9.50 days (range, 5 to 45 days); 45 (76.27%) cases of endotheliitis developed within 30 days. The multadjusted hazard ratio (HR) associated with increased risk of endotheliitis was 16.1 (95% CI, 3.9 to 66.9; $P < 0.001$) for patients 76 years of age or older and 10.2 (95% CI, 2.4 to 43.2; $P = 0.002$) for those 66 to 75 years of age compared with those 65 years of age or younger. Endotheliitis was also associated with history of diabetes mellitus (HR, 1.9; 95% CI, 1.1 to 3.2; $P = 0.026$).

CONCLUSIONS. This study found the incidence of endotheliitis after cataract surgery to be 0.28%. Diabetes mellitus and old age are major risk factors for developing endotheliitis.

Keywords: endotheliitis, cataract surgery, risk factors

Corneal endotheliitis was first described by Khodadoust and Attarzadeh in 1982 and was designated as idiopathic immune corneal endotheliopathy.¹ It is characterized by corneal edema, keratic precipitates (KPs), and occasional anterior chamber reaction. More recently, corneal endotheliitis is thought to be a viral infection.^{2–6} Viral reactivation is thought to be associated with several types of stimuli such as psychologic stress, febrile illness, respiratory tract infection, and ocular trauma. Surgical trauma can lead to infection in cases with no previous history of viral eye disease.^{7–12}

Endotheliitis following cataract surgery is a rare condition.¹³ Herein, we examined a large cohort of patients who underwent cataract surgery and subsequently developed postoperative endotheliitis, providing insights into the incidence and potential risks factors of this disease.

METHODS

Study Design and Patients

This is a single-center retrospective cohort study. This study followed the tenets of Declarations of Helsinki and was approved by ethics committee of eye hospital of Wenzhou Medical University. Informed consent of patients was not required by the ethics committee.

Clinical records from the electronic medical record system (EyeCare System, V.15.11.26.2011; Thiseye, Wenzhou, China) of the Eye Hospital of Wenzhou Medical University were surveyed. The data for all patients who underwent uneventful cataract surgery between January 2015 and December 2016 were collected. Those who underwent combined procedures, such as keratoplasty or trabeculectomy, were excluded in the study. Patients with a history of keratitis or other corneal disease and patients with previous intraocular surgeries or cataract surgery performed elsewhere were also excluded.

All diagnoses of endotheliitis were individually confirmed by a senior corneal ophthalmologist using a combination of medical records, slit-lamp photographs, and in vivo confocal microscopy (IVCM). The diagnostic criteria were (1) symptoms of blurred vision, foreign body sensation, and/or irritation; (2) reduced visual acuity compared with last follow-up; (3) slit-lamp evidence of KPs and overlying stromal edema, with or without anterior chamber reaction; (4) endothelial morphologic changes detected by IVCM^{14,15}; and (5) complete resolution of signs and symptoms following antiviral treatment.

Data Collection

We completed a data collection sheet for each patient that included the following information: age at presentation, sex,



diabetes mellitus (DM), systemic hypertension, surgical technique, visual acuity at all follow-ups, IOP at all follow-ups, and treatment(s) attempted. Those patients who underwent cataract surgery in the second eye during the study period had both eyes included, and data on individual eyes were treated as independent units for the purpose of analysis. In addition, data related to endotheliitis were recorded, including affected eyes, time interval to first recording of endotheliitis, visual acuity before and at presentation of endotheliitis, IOP at presentation, slit-lamp photographs, and IVCN image.

Preoperative and Postoperative Management

All patients received standard preoperative care based on the institution's protocol. Patients received topical 0.5% levofloxacin eye drops (Santen Pharmaceutical, Osaka, Japan) six to eight times on the day prior to surgery in the eye undergoing surgery. After surgery, all patients were prescribed topical 1% prednisolone acetate (Pred-Forte; Allergan, Irvine, CA, USA) in tapering dosages for a 30-day postoperative period.

Patients presenting with postoperative endotheliitis were treated with topical 1% prednisolone acetate four times per day, 0.15% ganciclovir gel (Keyi Co., Wuhan, China) four times per day, and systemic acyclovir 400 mg five times per day or systemic valacyclovir 500 mg two times per day. The systemic antiviral agent was replaced by ganciclovir 1000 mg three times per day in cases without improvement after 1 week of treatment with valacyclovir or acyclovir.

Statistical Analysis

All statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Cox proportional hazard regression analyses, both univariate and multivariate, were used to calculate hazard ratios (HRs) with a confidence intervals (CI) of 95% for the potential risk factors. Univariate models were initially performed to test individual predictors and were subsequently entered in the multivariate model for predictors with $P < 0.25$ in a forward stepwise manner. The variable with the higher P value was sequentially removed until only variables with $P < 0.05$ remained in the model.

RESULTS

During the study period between January 2015 and December 2016, an initial dataset was collected on a total of 22,935 eyes. After the process of filtering, 20,743 eyes were included, including 18,980 cases of phacoemulsification and 1763 cases of extracapsular cataract extraction (ECCE; Fig. 1). The mean age \pm SD of the entire cataract surgery population was 69.9 \pm 10.5 years (range, 38 to 100 years). Fifty-nine eyes of 50 patients with a mean age of 76.2 \pm 7.1 years (range, 62 to 90 years) developed endotheliitis after cataract surgery. This resulted in an incidence of 0.28%. Endotheliitis occurred in 56 eyes (0.3%) after phacoemulsification and 3 (0.17%) eyes after ECCE.

Univariate analysis was performed on all preselected risk factors including sex, age, affected eyes, DM, hypertension, type of surgery, and abnormal IOP after surgery. Age and DM were significant risk factors for endotheliitis (Table 1).

The incidence of endotheliitis was 0.45% in patients with DM, carrying almost a two-fold increased risk for endotheliitis (hazard ratio [HR], 1.9; 95% CI, 1.1 to 3.2; $P = 0.026$). The risk of endotheliitis was higher for older than younger patients (0.03%, 0.32%, and 0.49% for patients ≤ 65 , 66 to 75, and ≥ 76 years, respectively). The multiaadjusted HR associated with increased risk of endotheliitis was 16.1 (95% CI, 3.9 to 66.9; P

< 0.001) for patients 76 years of age or older and 10.2 (95% CI, 2.4 to 43.2; $P = 0.002$) for those 66 to 75 years of age compared with those 65 years of age or younger. Table 2 presents the multivariate Cox proportional hazard model analysis of the two risk factors of endotheliitis. The survival curve for the relationship between the two risk factors and the development of endotheliitis is shown in Figure 2.

Table 3 shows the summary of demographic and clinical characteristics of patients with endotheliitis. The mean interval between surgery and first recording of endotheliitis was 24.51 \pm 9.50 days, with a range of 5 to 45 days. Forty-five (76.27%) cases of endotheliitis developed within 30 days. Eyes with postoperative endotheliitis had reduced visual acuity ranging from one to seven lines compared with last follow-up. Among them, 37 (62.71%) eyes decreased within three lines. Visual acuity of each eye was restored to preonset levels after resolution of endotheliitis. Nine (15.25%) eyes showed high IOP (> 21 mm Hg) at the time of diagnosis of keratitis and were restored to normal after resolution of endotheliitis. Forty-nine (83.05%) eyes resolved after treatment with valacyclovir or acyclovir. Ten (16.95%) eyes had no improvement with valacyclovir or acyclovir treatment but healed after treatment with ganciclovir.

Bilateral endotheliitis occurred in nine patients (four males, five females), all of whom underwent phacoemulsification. The mean age was 73.1 \pm 7.9 years (range, 62 to 85 years). Three of these patients were diabetics. The timing of onset of endotheliitis following surgery was similar between two eyes of the same patient.

According to the slit-lamp photographs, there were major two patterns of endotheliitis after cataract surgery (Fig. 3): mild type (38 eyes, 64.41%) and severe type (21 eyes, 35.59%). The former was characterized by mild corneal edema with Descemet's folds, KP(s), and pseudoguttata in corneal endothelium by IVCN. The latter revealed diffuse corneal edema and KP(s), with or without epithelial defect. No statistically significant differences were observed between the two types in age, diabetes, surgical technique, or other potential risk factors.

DISCUSSION

A variety of factors such as trauma, emotional or psychological stress, and menstruation have been suggested as potential triggers for reactivation in patients with latent viral infection.¹⁶ Previous reports observed that surgical trauma can cause infection in a case with no previous history of viral eye disease.^{17,18} Tan et al.⁷ reported the occurrence of corneal endotheliitis 3 weeks following laser in situ keratomileusis. Viral endotheliitis or keratitis after cataract surgery has previously been described in the literature. Barequet¹⁹ described herpes simplex keratitis occurring 1 to 5 weeks after cataract surgery in patients with no previous herpetic infection. A similar case was also described by Miyajima et al.,²⁰ with additional confirmation of herpes simplex virus (HSV) DNA detected using PCR. On the other hand, coxsackievirus has been known to cause endotheliitis 4 days after cataract surgery.¹⁷

The delayed onset of inflammation 4 to 35 days from the time of surgery is a common trait in corneal endotheliitis^{19,21-23}; a finding that was reflected in our study. We found that endotheliitis occurred in 0.28% of patients following cataract surgery. The time interval between surgery and first recording of endotheliitis was 5 to 45 days, most of which were within 30 days. In consideration of the time from onset of symptoms to presentation at the hospital, median period from surgery to onset of endotheliitis was shorter than 24.51 \pm 9.50

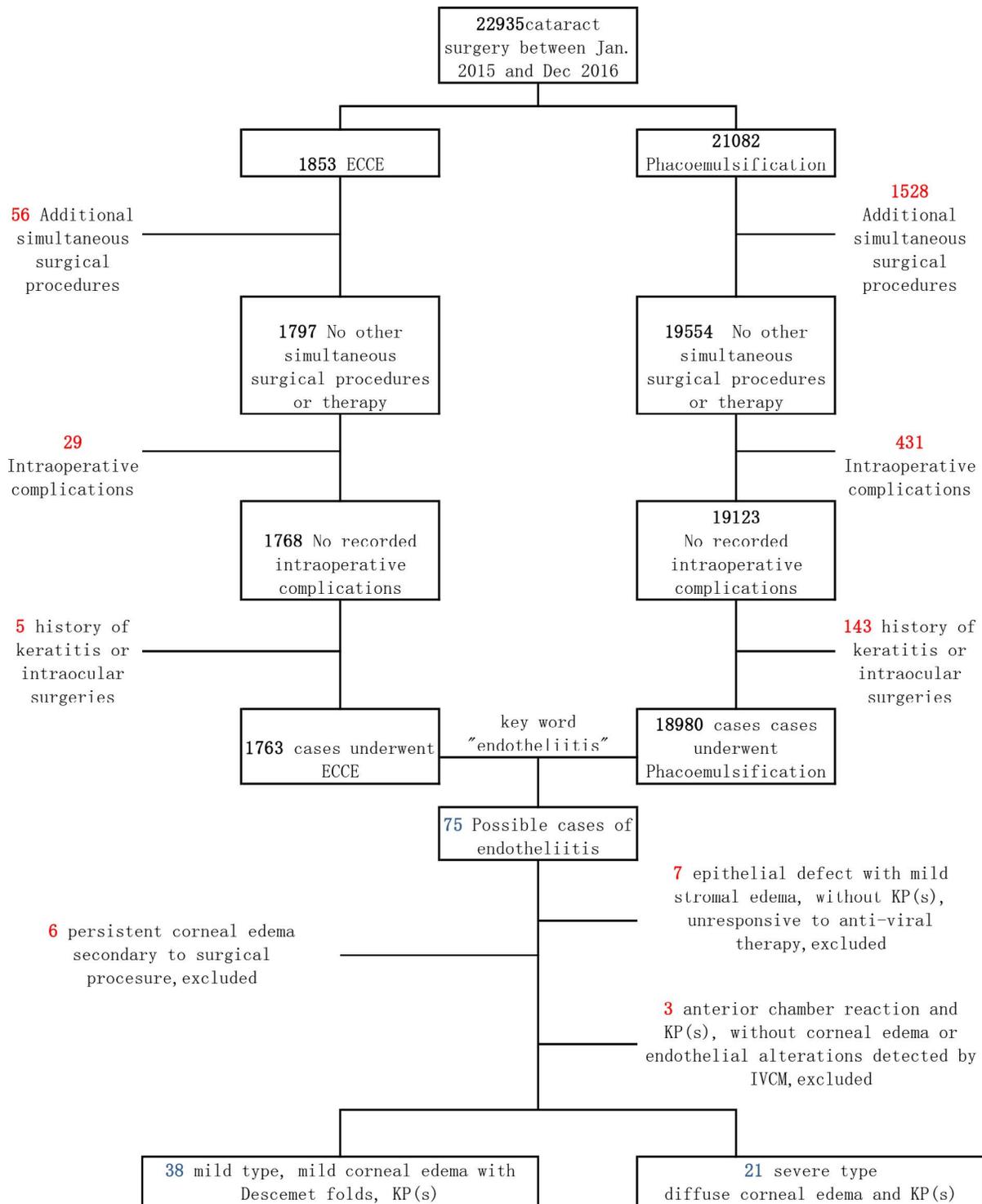


FIGURE 1. Flowchart showing filtering strategy. *Bold* numbers show eyes in ECCE and phacoemulsification group. Numbers in *blue* indicate eyes in filtering strategy of endotheliitis. Numbers in *red* show excluded eyes at each stage.

days. Our findings are in agreement with previously reported interval of 4 to 35 days.^{19,21-23} Because of the short interval between the surgical procedure and the onset of endotheliitis, this study suggests a possible relationship between cataract surgery and endotheliitis. It is possible that a preexisting latent virus might be reactivated by surgical trauma, as a result of the corneal incisions in conjunction with intensive treatment with topical corticosteroids used postoperatively. Several reports

have suggested that both cytomegalovirus endotheliitis and ocular surface herpetic disease may be associated with DM and that viral infection is more common among patients with DM.^{24,25} Our data reveal that patients with DM have a significantly higher incidence of endotheliitis than patients without DM. This may be due to abnormalities in cell-mediated immunity associated with hyperglycemia.^{26,27} Another possibility could be that the blood-aqueous barrier in patients with

TABLE 1. Univariate Cox Proportional HR of Potential Risk Factors to Onset Endotheliitis After Cataract Surgery

Risk Factors	Cataract Surgeries (No. of Eyes)	Endotheliitis (No. of Eyes)	Incidence (%)	HR	P
Sex					
Males	8,618	31	0.36		
Females	12,125	28	0.23	1.3 (0.8-2.1)	0.357
Type of surgery					
Phaco	18,980	56	0.30		
ECCE	1,763	3	0.17	0.6 (0.2-1.8)	0.352
IOP after surgery, mm Hg					
≤21	16,261	50	0.31		
>21	4,482	9	0.20	0.7 (0.3-1.3)	0.239
DM					
Yes	4,263	19	0.45		
No	16,480	40	0.24	1.8 (1.1-3.2)	0.029*
Hypertension					
Yes	9,546	32	0.33		
No	11,197	27	0.24	1.4 (0.8-2.3)	0.207
Age, y					
≤65	6,520	2	0.03		
66-75	7,412	24	0.32	10.6 (2.5-44.7)	0.001*
≥76	6,811	33	0.49	15.8 (3.8-66.0)	0.000*

* Statistically significant ($P < 0.05$).

DM is weakened, and virus-infected cells may move more easily into the corneal cells.²⁸

Our study found that there was significantly higher incidence of endotheliitis for older than younger patients. This finding is consistent with an epidemiologic study by Stanzel et al. that reported an increase in incidence of herpes simplex keratitis with age, peaking in patients with age over 75 years.²⁹ Another study conducted by Koizumi et al. also indicated that cytomegalovirus (CMV) endotheliitis is more common in elderly population.³⁰

Topical steroid use during HSV keratitis has been proven to be pernicious due to associated immunosuppression, facilitation of HSV transfer through corneal cell layers, and increasing cell susceptibility to HSV infection.³¹⁻³³ Previous studies have suggested endotheliitis may be related to intensive use of topical steroids causing local immunosuppression.^{13,18} In this study, intensive use of steroids after surgery might have led to the development of endotheliitis following cataract surgery. The pathogenesis of endotheliitis involves direct viral invasion and immune reaction. Although steroids help to reduce inflammation following cataract surgery, this may in fact be a major contributing factor to the etiology of postoperative endotheliitis.

The impact of phacoemulsification energy on the cornea generally causes onset of corneal edema intraoperatively or immediately after cataract surgery. In our study, all eyes had clear transparent cornea postoperatively until the onset of endotheliitis. The interval between onset of endotheliitis and cataract surgery was approximately 24 days. It would be

unlikely that the effect of energy could cause this subacute presentation lasting for a long period. In addition, three cases developed endotheliitis after ECCE. Thus, the onset of endotheliitis is less likely to be related to this factor.

Our study included a small group of patients who developed endotheliitis bilaterally following surgery in each eye over a short timeframe. The inclusion of both eyes from a single patient may result in some bias as this group may inherently be predisposed to developing the disease already. We analyzed this group separately and found that the timing of disease onset was no different statistically compared to patients with disease in one eye only.

TABLE 3. Summary of Demographic and Clinical Characteristics of All Endotheliitis Cases

Characteristics	No. (%)
Sex	
Male	31 (52.54)
Female	28 (47.46)
Affected eyes	
Right	25 (42.37)
Left	34 (57.63)
Type of surgery	
Phaco	56 (94.92)
ECCE	3 (5.08)
Time interval to onset, days	
≤30	45 (76.27)
>30	14 (23.73)
Decrease of visual acuity	
≤3 lines	37 (62.71)
>3 lines	22 (37.29)
IOP	
Normal	50 (84.75)
Elevated	9 (15.25)
Treatment	
Valaciclovir/acyclovir	49 (83.05)
Ganciclovir	10 (16.95)

TABLE 2. Multivariate Cox Proportional HR of Risk Factors to Endotheliitis With Adjustment for Intrasubject Correlation

Risk Factors	HR (95% CI)	P
DM	1.9 (1.1-3.2)	0.026
Age, y		
≤65	1.00	
66-75	10.2 (2.4-43.2)	0.002
≥76	16.1 (3.9-66.9)	0.000

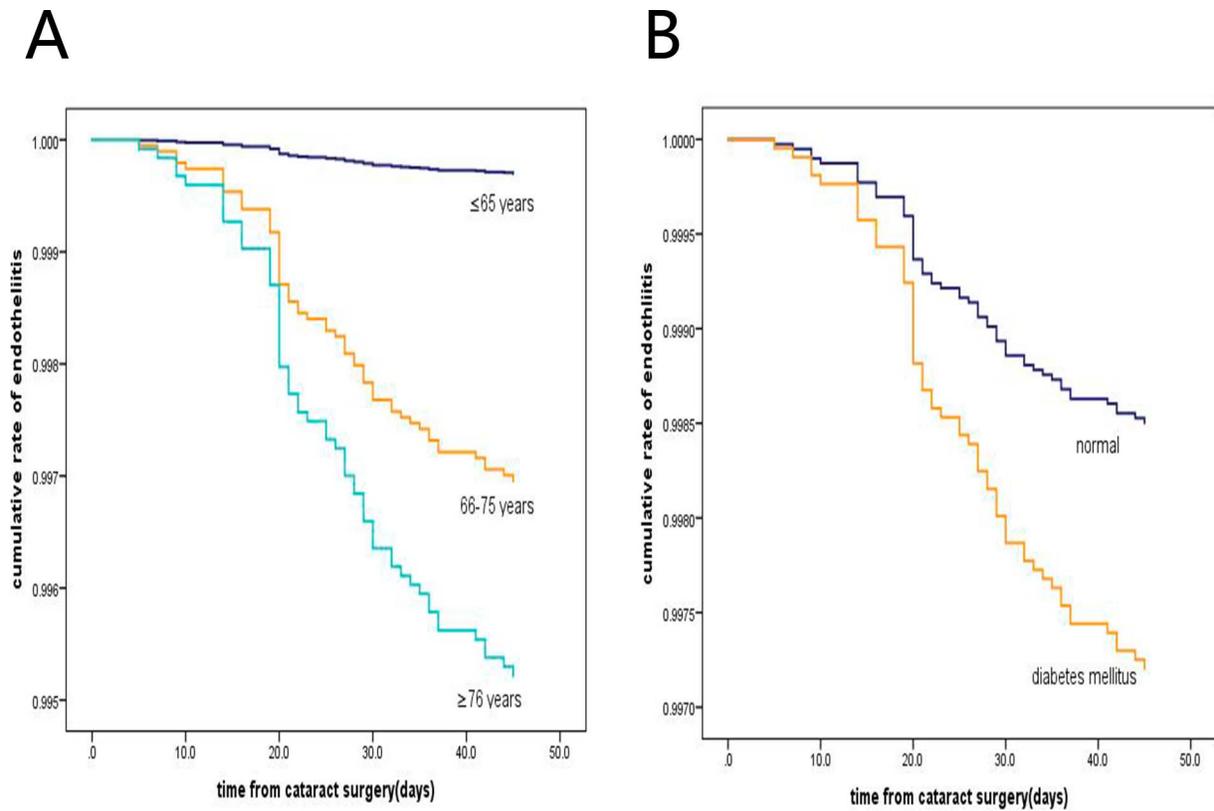


FIGURE 2. Cox proportional HR of the risk factors of viral endotheliitis since cataract surgery by days: (A) Age, ≤ 65 , 66 to 75 and ≥ 76 years and (B) DM.

Topical ganciclovir 0.15% has been shown to be useful in the treatment of CMV endotheliitis,^{34,35} reducing CMV viral load in the aqueous. It has also been reported to be effective in treating herpes keratitis.³⁶ Given these findings in the literature and that both CMV and HSV are common causes of

endotheliitis, we believe there is a role for topical ganciclovir in these cases as it provides additional benefit in covering both viral etiologies.

There are several limitations of our study. Although viral detection was not acquired in this cohort, patients displaced

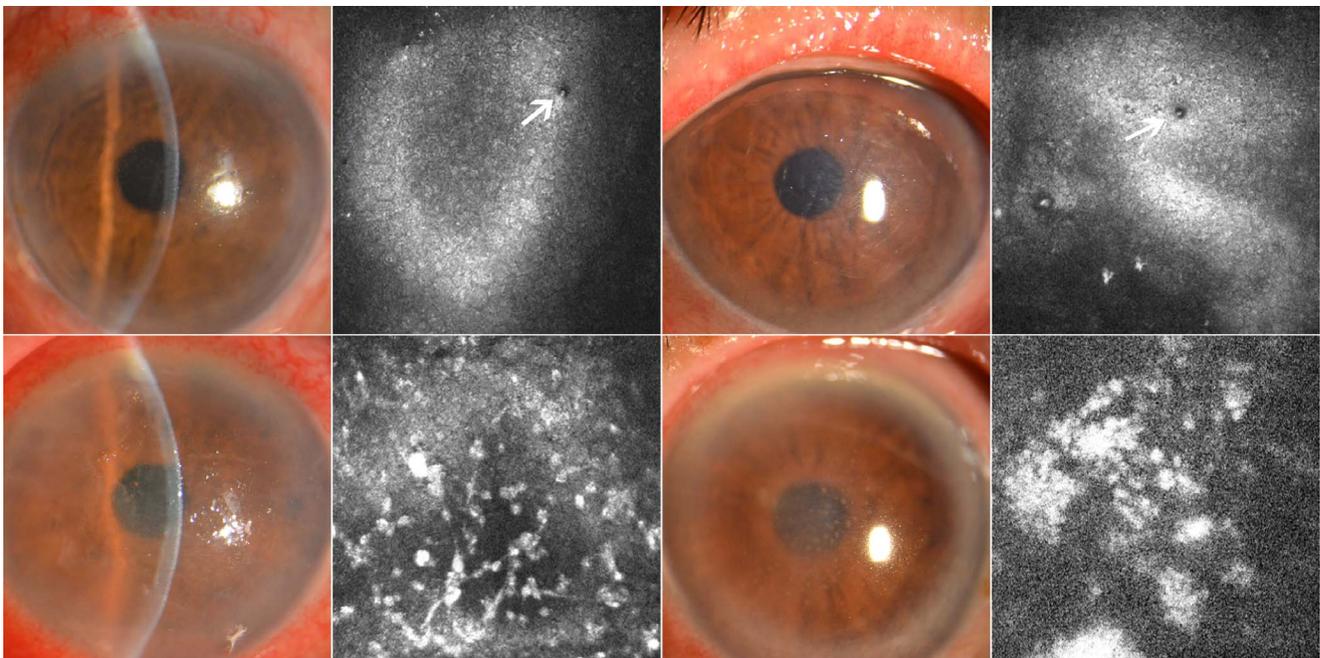


FIGURE 3. Two different types of endotheliitis after cataract surgery: (Top) Slit-lamp photograph showing mild corneal edema with Descemet's folds, KP(s), and pseudoguttata (arrows) in corneal endothelium by IVCN. (Bottom) Diffuse corneal edema and endothelial alterations detected by IVCN.

signs and symptoms consistent with the disease and showed complete resolution of signs and symptoms with antiviral treatment. There are many laboratory tests for detection of virus or viral antigen, such as viral culture, enzyme linked immunosorbent assay (ELISA), and PCR. However, neither viral culture nor ELISA has been proven to be sensitive enough to establish a viral etiology.^{37,38} PCR is widely used to detect etiologic agents in the aqueous humor. However, given the positive clinical response to treatment and the inherent low positive rate of PCR in endotheliitis^{39,40} with poor disease correlation,⁴¹ our patients were not subjected to anterior chamber tapping. The diagnosis of endotheliitis is largely based on clinical features in general,⁴² whereas PCR allows further identification of the causative viral agent. Although we may not have PCR confirmation of a viral cause, all patients who presented with these clinical criteria responded well to antiviral treatment.

In summary, this study reports the characteristics and risk factors of endotheliitis after cataract surgery. Our study found the incidence of endotheliitis to be 0.28%. The key risk factors were age and DM.

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