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Prevalence and risk factors of dry eye patients with corneal epithelial defects: A hospital - based retrospective study

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干眼角膜上皮损伤患者患病率和危险因素的回顾性研究

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摘要

目的:探究干眼角膜上皮损伤患者的流行病学特征及相关危险因素。

方法:回顾 2018-07/2019-06 期间就诊于北京大学第三医院的干眼角膜上皮损伤患者的门诊病历,对患者性别、年龄、就诊日期、合并症以及同一时期的气象指标进行统计学分析。

结果:回顾性分析 291 名干眼角膜上皮损伤患者,其中有 75.3%为女性。21-30 岁的青年患者占比最大(26.5%),青少年(<18 岁,5.8%)和老年人(≥61 岁,17.2%)较少。然而,中青年患者虽然占比较大,其平均就诊次数较少(5.4±12.4)。春季和冬季是最主要的就诊季节。分析表明,PM_{10}、二氧化硫(SO_2)、二氧化氮(NO_2)、以及较低的平均相对湿度与干眼角膜上皮损伤显著相关($P<0.05$)。结膜炎、白内障、视物模糊以及倒睫是排名前四位的合并症。

结论:女性、青年人群干眼角膜上皮损伤问题不容忽视。PM_{10}、SO_2、NO_2 和空气湿度降低与干眼角膜上皮损伤显著相关。对于合并有结膜炎、白内障、视物模糊以及倒睫的干眼患者,更应关注其角膜状况。

关键词:合并症;角膜上皮缺损;干眼症;流行率;风险因素

Abstract

• AIM: To analyze the characteristics and correlated risk factors of dry eye patients with corneal epithelial defects.

• METHODS: Outpatient medical records of dry eye patients with corneal epithelial defects at Peking University Third Hospital from July 2018 to June 2019 were retrospectively analyzed. The patients' data including sex, age, visit date, presence of comorbidities, and meteorological indicators at the same period were statistically analyzed.

• RESULTS: A total of 291 dry eye patients with corneal epithelial defects, of whom 75.3% were female, were retrospectively analyzed. Young patients aged 21-30 made up the most (26.5%), while the proportion of teenagers (<18 years, 5.8%) and the elderly (≥61 years, 17.2%) was low. However, as the largest proportion of this population, young and middle-aged patients tend to experience fewer visits (5.4±12.4). Spring and winter were the main seasons of complaints. The meteorological indicators at the same period including fine-particulate matter with a median aerometric diameter of less than 10μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and reduced average relative humidity were found significantly correlated with dry eye corneal epithelial defects ($P<0.05$). Conjunctivitis, cataracts, blurred vision, and trichiasis ranked the top four comorbidities.

• CONCLUSION: Dry eye corneal epithelial defects of young and female population cannot be ignored. PM_{10}, SO_2, NO_2, and reduced humidity are found significantly correlated with dry eye corneal epithelial defects. For dry eye patients with conjunctivitis, cataracts, blurred vision, and trichiasis, more attention should be paid to their corneal conditions.

• KEYWORDS:comorbidity; corneal epithelial defects; dry eye; prevalence; risk factor
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INTRODUCTION

Dry eye disease (DED) refers to a chronic multifactorial condition of the ocular surface due to a loss of homeostasis of the tear film, which may involve lacrimal glands, meibomian glands, and corneal innervations, leading to varying degrees of discomfort and visual disability[1-3]. DED is one of the most prevalent diseases for patients to seek ophthalmological care[3-4]. According to Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS) II report, prevalence rates of symptomatic DED range from 6.5% to 52.4% around the world[5]. And it was 31.4% among Chinese people aged 5 - 89 years[6], which causes a great social burden.

The cornea is an important refractive medium, whose health and transparency are important for maintaining good visual function[7]. With 5 to 7 squamous epithelial cell layers, corneal epithelium plays an important role in resisting external adverse environmental factors and injuries[3]. An unhealthy tear film can affect the state of the corneal surface[8-9], resulting in more exposure of the cornea to unfavorable environmental factors such as ultraviolet radiation and harmful pollutants, which may cause oxidative stress and chronic inflammation in corneal epithelial cells[3]. As the cornea has a rich supply of sensory innervation and neuro-mediators which permit neuro-epithelial interaction, corneal epithelial defects may have an important impact on the subjective discomfort of patients with dry eye resulting in pain and tearing, thus affecting visual function and quality of life[10-13]. If corneal epithelial defects of dry eye are not treated in time, it may cause more severe damage and possibly even blindness[14].

There have been many studies focused on the risk factors of DED around the world. Previous studies have shown that female and advanced age represent risk factors in the progression of DED[6, 15]. Environmental factors such as wind and lower humidity, and exposure to air pollutants such as carbon monoxide (CO), nitrogen dioxide (NO_2), and fine-particulate matter with a median aerometric diameter of less than 2.5 μm ($PM_{2.5}$) can also aggravate dry eye development and corneal defects[16-19]. Additionally, the onset of dry eye has obvious seasonal characteristics, usually in allergic, dry, and cold seasons[17, 20-22]. However, to our best knowledge, there has been no study specifically analyzing risk factors of dry eye patients with corneal epithelial defects. The purpose of the present study was to retrospectively analyze the characteristics of dry eye patients with corneal epithelial defects at Peking University Third Hospital and explore what kind of dry eye patients are prone to corneal involvement and its risk factors, to provide more valuable clues on the analysis of features, mechanism, and management of dry eye corneal epithelial defects.

SUBJECTS AND METHODS

Study Population This is a hospital-based retrospective study. A retrospective analysis of outpatient medical records of dry eye patients with corneal epithelial defects at the Department of Ophthalmology in Peking University Third Hospital from July 2018 to June 2019 was conducted for this study. The scientific research big data system of Peking University Third Hospital was used to retrieve related cases. Patients' medical records with the 1) primary diagnosis of dry eye, dry eye disease, or keratoconjunctivitis sicca; 2) ocular physical examination presented positive corneal staining, corneal epithelial staining, or corneal epithelial defects, including both dot-like defects and erosions, were included, and those with ocular trauma or corneal trauma were excluded. This study followed the principles of the Declaration of Helsinki and was approved by Peking University Third Hospital Medical Science Research Ethics Committee (IRB00006761-M2020432).

Ethical Approval This study was approved by Peking University Third Hospital Medical Science Research Ethics Committee (IRB00006761 - M2020432). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Data Collection Patients' basic characteristics were retrieved including gender, age, visit date, number of visits, previous history, and diagnosis. The symptoms and physical examination results were also recorded such as visual acuity, intraocular pressure, conjunctival congestion, meibomian gland conditions, corneal staining result, and tear break-up time. Patients' comorbidities were also collected for analysis. Meteorological factors at the parallel period were obtained from the China Meteorological Data Service Center website (http://data.cma.cn), including average relative humidity, average temperature, average 2-minute wind speed, fine-particulate matter with a median aerometric diameter of less than 10 μm (PM_{10}), $PM_{2.5}$, sulfur dioxide (SO_2), CO, NO_2, ozone (O_3) and air quality index (AQI), to analyze the correlation between weather conditions and dry eye corneal epithelial defects. The time of meteorological variables were collected corresponded with time of diagnosis. All data were extracted by one researcher based on medical records using a standard form, and then double checked by another researcher. All personally identifiable information of patients

was treated with strict secrecy and used for research purposes only.

Statistical Analysis Data analysis was performed using SPSS 23.0. Shapiro-Wilk test was used for normality test. $P>0.05$ was considered to conform to the normal distribution. Continuous variables were analyzed using t-test for equality of means in samples with normality and homogeneity of variance, nonparametric Mann-Whitney U test for two independent samples without normal distribution, and nonparametric Kruskal-Wallis test for more than two independent samples which were non-normally distributed. Categorical data were compared using the Chi-square test for samples with normality and homogeneity of variance. Spearman's rho nonparametric correlation test was used for correlation analysis between the number of cases and the weather. $P<0.05$ was considered to be statistically significant in most conditions, except that in Kruskal-Wallis test $P<0.001$ was considered statistically significant.

RESULTS

A total of 291 dry eye patients with corneal epithelial defects were included in this study. The difference between the number of male (72, 24.7%) and female (219, 75.3%) was significant [$\chi^2(1, n=291)=74.258$, $P<0.001$]. Patients' basic characteristics were listed in Table 1.

Age Characters and Distribution The average age was 40.9±18.2 years. Young and middle-aged patients made up the majority (77%), especially those aged 21-30 accounting for 26.5%. However, the proportion of the elderly and teenagers (≥61 years or <18 years) was low (5.8% and 17.2% respectively). There was no significant difference in the proportion of males and females under the age of 18 years old [$\chi^2(1, n=17)=0.529$, $P=0.467$], while females accounted for a greater proportion in adults aged 18 ~ 60 [$\chi^2(1, n=224)=66.446$, $P<0.001$] and senior people over 60 [$\chi^2(1, n=50)=15.680$, $P<0.001$]. The age distribution of patients was presented in Figure 1, and the results of Chi-square test between males and females were listed in supplementary Table 1S. Taken together, compared to the elderly and teenagers, the number of young female dry eye patients with corneal involvement was larger.

Outpatient visits features The average number of outpatient visits within one year was 7.3±13.7. 73.2% of outpatients visited no more than 5 times in one year, while the rest visit 5 times or more. The highest number of visits reached 142. A statistically significant difference was found between the number of male and female in patients with fewer than 10 visits [$1\leqslant n\leqslant 5$, $\chi^2(1, n=213)=66.484$, $P<0.001$; $6\leqslant n\leqslant 10$, $\chi^2(1, n=29)=15.207$, $P<0.001$], but not in patients with more than 10 visits [$11\leqslant n\leqslant 15$, $\chi^2(1, n=11)=0.818$, $P=0.366$; $n\geqslant 16$, $\chi^2(1, n=38)=0.421$, $P=0.516$]. Although young patients made up the majority, the number of their visits was significantly lower than that of the elderly and teenagers (≥61 years or <18 years; $P<0.001$; Figure 2). The distribution of patient visit date was presented in Figure 3. Patients tend to seek medical help in spring and winter. The number of cases from June to September was at a very low level, while that from November to May (except February) was large. Overall, the visits frequency of dry eye with corneal epithelial defects was high, especially in spring and winter.

Comorbidities Based on outpatient medical records, comorbidities of these patients were listed in supplementary Table 2S. Conjunctivitis, cataract, blurred vision, and trichiasis ranked the top four among all comorbidities. The visit date of patients with conjunctivitis showed seasonality. There were 8 patients with conjunctivitis in March, which accounted for the most.

Correlations with meteorological factors Meteorological factors at the parallel period were obtained from the China Meteorological Data Service Center website (http://data.cma.cn), including average relative humidity, average temperature, average 2 minute wind speed, fine-particulate matter with PM_{10}, $PM_{2.5}$, SO_2, CO, NO_2, O_3 and AQI. Correlation coefficient (CC) and P value between the number of cases and meteorological factors was shown in Figure 4. Dry eye corneal epithelial defects were found significantly correlated with PM_{10} (CC=0.814, $P=0.001$), SO_2 (CC=0.597, $P=0.040$), NO_2 (CC=0.578, $P=0.049$) and reduced average relative humidity (CC=-0.627, $P=0.029$). No correlations were found with average temperature (CC=-0.462, $P=0.130$), average 2 minute wind speed (CC=0.477, $P=0.117$), $PM_{2.5}$ (CC=0.343, $P=0.275$), CO (CC=-0.084, $P=0.795$), O_3 (CC=-0.270, $P=0.397$) and AQI (CC=0.575, $P=0.050$).

DISCUSSION

Corneal epithelial defects have an important influence on the subjective discomfort of dry eye patients. If it is not treated in time, more severe damage and even blindness can be caused[14]. Previous studies have provided much information on the population characteristics and risk factors of DED, but we knew very little about these factors specifically for dry eye corneal epithelial defects. This study retrospectively analyzed the correlated factors of dry eye patients with corneal epithelial defects who attended Peking University Third Hospital from July 2018 to June 2019. We discovered that young female patients made up the largest proportion, while the elderly tend to experience more visits. Spring and winter were the main seasons of complaints. PM_{10}, SO_2, NO_2, and reduced average relative humidity were found correlated with dry eye corneal epithelial defects. Conjunctivitis, cataracts, blurred vision, and trichiasis ranked the top four comorbidities.

As summarized in TFOS DEWS II report, female sex has been regarded as one of the risk factors for DED[23]. Females tend to have a higher incidence and more obvious symptoms and signs of DED[15, 23]. Previous studies have reported that about

Table 1 Patient characteristics

Patient characteristics	Male	Female	Total	P^d
Number of patients (n ,%)	72 (24.7)	219 (75.3)	291	<0.001[a,d]
Age (years,$\bar{x}\pm s$)	37.5±20.8	42.0±17.2	40.9±18.2	0.070[b]
<18 (n, %)	10 (58.8)	7 (41.2)	17 (5.8)	0.467[a]
18~60 (n, %)	51 (22.8)	173 (77.2)	224 (77.0)	<0.001[a,d]
≥61 (n, %)	11 (22.0)	39 (78.8)	50 (17.2)	<0.001[a,d]
Outpatient visits (n, $\bar{x}\pm s$)	9.2±12.2	6.6±14.1	7.3±13.7	0.426[c]
1~5 (n, %)	47 (22.1)	166 (77.9)	213 (73.2)	<0.001[a,d]
6~10 (n, %)	4 (13.8)	25 (86.2)	29 (10.0)	<0.001[a,d]
11~15 (n, %)	4 (36.4)	7 (63.6)	11 (3.8)	0.366[a]
≥16 (n, %)	17 (44.7)	21 (55.3)	38 (13.1)	0.516[a]
Visual acuity				
OD (LogMAR,$\bar{x}\pm s$)	0.168±0.294	0.182±0.257	0.187±0.246	0.557[c]
OS (LogMAR,$\bar{x}\pm s$)	0.108±0.134	0.161±0.206	0.180±0.222	0.032[c,d]

[a]Chi-square test; [b]t-test for Equality of Means; [c]independent-samples Mann-Whitney U test; [d]P<0.05 comparing male and female.

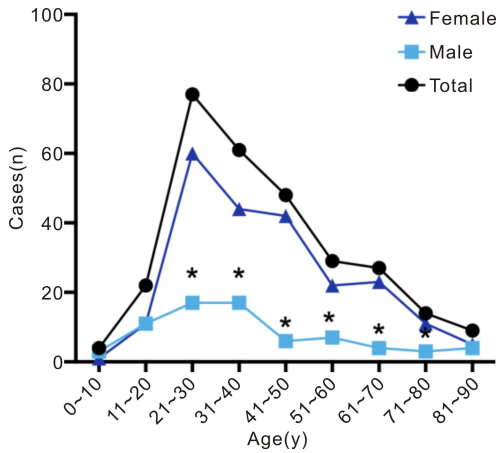

Figure 1 Age distribution. *P<0.05 for sex ratio (Chi-square test).

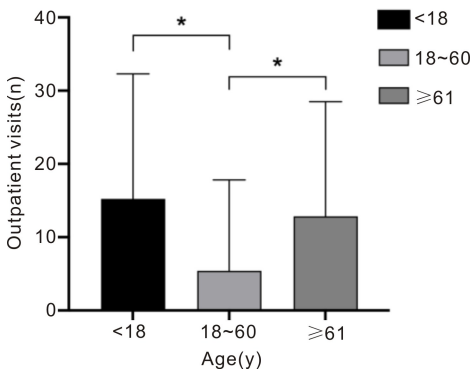

Figure 2 Number of visits by age. *P<0.001 for outpatient visits of different age groups (independent-samples Kruskal-Wallis test).

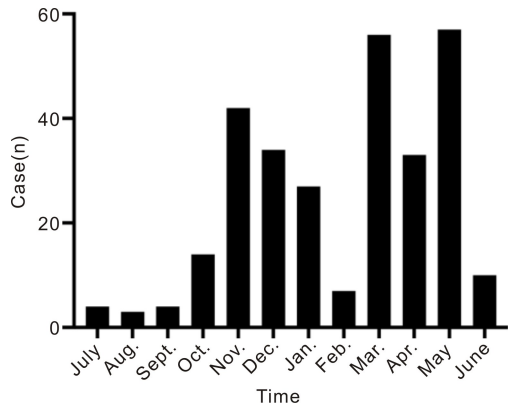

Figure 3 Visit date distribution.

Table 1S Results of Chi-square test for age distribution between male and female

Age (years)	df	n	χ^2	P
0-10	1	4	1	0.317
11-20	1	22	0	1
21-30	1	77	24.013	<0.001[a]
31-40	1	61	11.951	0.001[a]
41-50	1	48	27.000	<0.001[a]
51-60	1	29	7.759	0.005[a]
61-70	1	27	13.370	0.001[a]
71-80	1	14	4.571	0.033[a]
81-90	1	9	0.111	0.739

[a]P<0.05 for sex ratio.

65.5% ~ 80.7% of dry eye patients were female[16-17, 21, 24]. Our study indicated that females (75.3%) were also more likely to experience dry eye corneal epithelial defects. One explanation is that hormone levels may affect the occurrence of DED and corneal conditions[23, 25]. It is reported that androgens can suppress inflammatory reactions and enhance the function of lacrimal and meibomian glands, and estrogen and progesterone may antagonize this effect[26-27]. Lower levels of androgens in women can lead to less secretion of tears, which makes the cornea more likely to be exposed to unfavorable environmental factors, resulting in a higher risk of dry eye corneal epithelial defects in females.

According to previous research, advanced age is associated with DED[5, 28]. A Japanese study showed that patients aged 50-59 had the largest proportion[29]. However, in this study, young and middle-aged patients made up the majority, indicating that among dry eye patients, perhaps young and middle-aged people are more likely to develop corneal epithelial defects. Working and using contact lenses by young and middle-aged people may also be the reason why they are

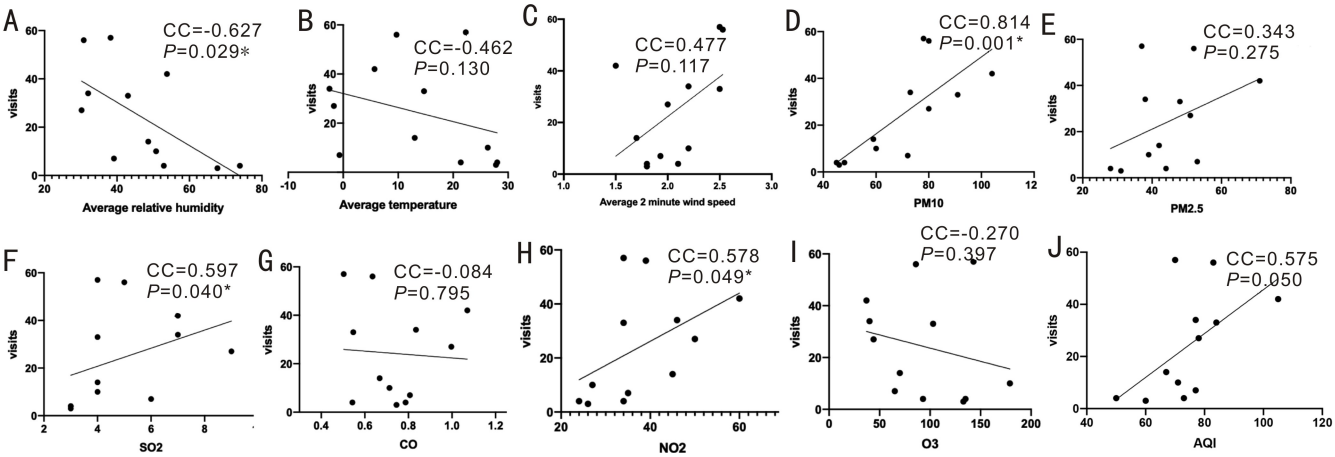

Figure 4 Correlation between the number of cases and meteorological factors (Spearman's rho nonparametric correlation test). PM_{10}: fine-particulate matter with a median aerometric diameter of less than 10 μm; $PM_{2.5}$: fine-particulate matter with a median aerometric diameter of less than 2.5 μm; SO_2: Sulfur dioxide; CO: Carbon monoxide; NO_2: Nitrogen dioxide; O_3: Ozone; AQI: Air quality index; CC: Correlation coefficient; $^*P<0.05$.

Table 2S Comorbidities of patients with dry eye corneal epithelial defects.

Comorbidities	Frequency (n)	Proportion (%)
Conjunctivitis	26	8.9
Cataract or after cataract surgery	18	6.2
Blurred vision	15	5.2
Trichiasis	12	4.1
Vitreous opacity	9	3.1
Glaucoma or suspicious glaucoma	7	2.4
Meibomian gland cyst or meibomian gland dysfunction	7	2.4
Keratitis, corneal ulcer or other corneal abnormalities	7	2.4
Shed tears	6	2.1
Conjunctival abnormalities	6	2.1
Graft versus host disease	3	1.0
Sjogren's syndrome	2	0.7
Pterygium	2	0.7
Blepharospasm	2	0.7
Eye pain or orbital pain	2	0.7
Macular degeneration	2	0.7
Blepharitis	2	0.7
Eyelid insufficiency	1	0.3
Thrombocytopenia	1	0.3
Hypertension	1	0.3
Refractive error	1	0.3
Ciliary syndrome	1	0.3
Diabetes	1	0.3
Neurotrophic keratoconjunctivitis	1	0.3

Conjunctival abnormalities include conjunctival concretion, subconjunctival hemorrhage, and conjunctivochalasis.

more prone to dry eye corneal epithelial defects.

Although young patients accounted for the majority in the present study, their average number of outpatient visits here was significantly lower than the elderly. First, this may indicate that their symptoms are less serious. Young people usually have better recovery and tolerance abilities. With aging, the level of androgens generally declines linearly in both males and females, and the tear secretion of lacrimal gland and the oil secretion of meibomian glands decreases, resulting in more evaporation, which leads to more severe symptoms in the elderly[4, 6, 26, 30]. Second, our results may be a suggestion that young people's awareness of seeking ophthalmological care is not so strong. They are usually too busy to see a doctor. We need to improve young patients' awareness of seeking medical treatment, especially for dry eye patients.

Previous studies have reported that meteorological factors may affect the occurrence of DED. Air humidity has long been considered an influencing factor for DED[16]. Tear evaporative rate and blink rate were reported higher in desiccating environments[31-32]. In concordance with previous studies, we discovered that relative humidity is negatively related to dry eye corneal epithelial defects. That may be the reason why our results showed dry eye corneal epithelial defects number went high in winter because of the lowest air humidity in winter in Beijing. Higher air humidity helps reduce the evaporation of tears, while on the contrary, winds and high temperatures might increase the evaporation of tears. It has been reported that wind and temperature are important factors affecting dry eye sensation and symptoms[16-17]. However, no correlation between temperature, average 2 minute wind speed and dry eye corneal epithelial defects was found in this study.

Another reason that number of dry eye corneal epithelial defects went high in winter may be that air pollution is heavy in winter in Beijing and is reported to be associated with DED and some other allergic diseases[16]. Our results showed that PM_{10}, SO_2, and NO_2 were significantly correlated with dry eye corneal epithelial defects. One possible explanation is that combustion products (such as SO_2 and NO_2) might change the structure of the tear film lipid layer[24]. A study in Hangzhou showed that DED was significantly associated with PM_{10}, $PM_{2.5}$, SO_2, NO_2, and CO[24]. And a study in Taiwan indicated that CO and NO_2 were related to DED[16]. What our study has in common with these previous studies is that we all discovered the correlation between air pollution and DED, however, PM_{10}, SO_2, and NO_2maybe more related to corneal conditions and recovery. The specific mechanism needs further study. Altogether, the results of our analysis further support that the DED corneal epithelial defects are closely related to air pollution. Health problems caused by environmental pollution should be taken seriously.

It was reported that the period of most severe symptoms of DED occurs during the season of high allergy and weather fluctuations[21-22]. In the present study, patients tend to seek ophthalmological care in spring and winter. Allergens such as pollen are more common in spring. Allergic conjunctivitis accounts for 90% of ocular allergy cases[33]. DED was reported to be related to allergic conjunctivitis, which is thought to be associated with instability of the tear film[34-35]. In this study, 8.9% of patients with dry eye corneal epithelial defects were associated with varying degrees and types of conjunctivitis. Increased allergens may be an important factor for the high number of cases in spring in Beijing despite relatively high air humidity.

In the present study, we retrospectively analyze the characteristics of dry eye patients with corneal epithelial defects. Several limitations existed in our study: First, even though we recruited 291 patients, it is a single-center retrospective study. Second, some outpatient medical records were not complete and lack of data on the corneal staining grading of patients, so we couldn't analyze the severity of corneal epithelial defects and its related factors. Third, the specific mechanisms why these basic characters and risk factors inducing corneal epithelial defects are not conducted or clarified in this study. In the future, larger prospective studies can be performed to further explore the characteristics and mechanisms of dry eye corneal epithelial defects.

In summary, our study retrospectively analyzed all dry eye patients with corneal epithelial defects in one year and indicated that 1) female patients with dry eye are more likely to experience corneal epithelial defects; 2) young patients have the largest proportion, while they tend to experience fewer visits; 3) dry eye corneal epithelial defects is more likely to occur in spring and winter, and is correlated with PM_{10}, SO_2, NO_2 and reduced average relative humidity; 4) conjunctivitis, cataracts, blurred vision and trichiasis ranked the top four among comorbidities. Therefore, in the process of diagnosis and treatment of dry eye patients, we should pay more attention to young and female patients in the spring and winter, and improve their awareness of seeking medical treatment. For dry eye patients with conjunctivitis, cataracts, blurred vision, and trichiasis, more attention should be paid to the condition of the cornea. Reducing PM_{10}, SO_2, NO_2 pollution and increasing air humidity may help improve the symptoms of dry eye corneal epithelial defects. To the best of our knowledge, this study analyzed the characteristics and possible environmental risk factors of dry eye patients with corneal epithelial defects for the first time. Our results add to the limited available data on the characteristics and risk factors of dry eye corneal epithelial defects, and will aid further mechanism research in the future.

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