Original Article

# Epidemic Keratoconjunctivitis in India: Trend Analysis and Implications for Viral Outbreaks

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**Purpose:** To describe the correlation between the temporal pattern of presentation of acute epidemic keratoconjunctivitis (EKC) of presumed adenoviral etiology with meteorological parameters such as environmental temperature, rainfall, humidity, and wind speed. **Methods:** This cross-sectional hospital-based study included 2,408,819 patients presenting between August 2010 and February 2020. Patients with a clinical diagnosis of EKC in at least one eye were included as cases. A smaller cohort of patients with acute (≤1 week) presentation hailing from the district of Hyderabad during the calendar years 2016–2019 was used to perform correlation analysis with the local environmental temperature, rainfall, humidity, and wind speed (data obtained from the Telangana State Development and Planning Society). **Results:** Overall, 21,196 (0.87%) patients were diagnosed with EKC, of which 19,203 (90.6%) patients had acute onset; among which the cohort from the district of Hyderabad included 1,635 (8.51%) patients. The mean monthly prevalence in this cohort was 0.89% with a peak prevalence in April (1.09%). The environmental parameters of rainfall ($r^2 = 0.47/P = 0.0131$), humidity ($r^2 = 0.65/P = 0.0014$), and wind speed ($r^2 = 0.56/P = 0.0047$) were significantly negatively correlated with the temporal pattern of EKC in the population. There was no visible trend or significant correlation seen with temperature ($r^2 = 0.08/P = 0.3793$). **Conclusion:** Contrary to popular belief, epidemic viral infections like EKC may not be affected by temperature, but rather by a complex interplay of other environmental factors such as humidity, rainfall, and wind speed. An increase in rainfall, wind speed, and humidity contributes to a lower prevalence of EKC cases during the year.

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The recent global pandemic of the coronavirus has sensitized the entire world to the importance of epidemiology and trend analysis. People all over the world are closely monitoring the rapidly changing landscape that reflects the aggressive nature of the novel coronavirus (COVID-19) pandemic that has engulfed the world affecting more than 183 countries at the time of this writing.[1] There are many myths associated with the spread of the virus that is being addressed by global agencies like the World Health Organization.[2] One of the popular speculative theories is the spread of the virus in varied climatic conditions with the notion that extreme climates may retard the same. The effect of a rise in the environmental temperature and the impact of the Indian summer on the spread of the virus needs to be ascertained in a local geographic setting. Among viruses relevant to ophthalmology, adenoviruses are probably the most commonly encountered type affecting the conjunctiva and cornea. The most frequent manifestation of ocular adenoviral infection is epidemic keratoconjunctivitis (EKC) followed by pharyngoconjunctival fever (PCF) with periodic outbreaks documented around the world.[3] In this context, the authors were interested to understand the temporal pattern of acute EKC of presumed adenoviral etiology which is one of the most common viral epidemics affecting humans annually. The authors intend to study the relationship between the effect of environmental factors such as temperature, humidity, rainfall, wind speed, and the prevalence of EKC in the population. This presents a unique insight into the temporal behavior of EKC and allows us the window of opportunity to learn in a geographic setting like India and is particularly relevant when the world is in the throes of a viral pandemic.

## Methods

### Study design, period, location, and approval

This cross-sectional observational hospital-based study included all patients presenting between August 2010 and February 2020 to an ophthalmology network located in 200 different geographical locations spread across 4 states (Telangana, Andhra Pradesh,

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Odisha, and Karnataka) of India.[4] The patient or the parents or guardians of the patient at the time of registration filled out a standard consent form for electronic data privacy. The study did not include any identifiable parameters of the patient during the analysis of the data. The study adhered to the Declaration of Helsinki and was approved by the institutional ethics committee. The clinical data of the comprehensive ophthalmic examination of each patient was entered into a browser-based electronic medical records system (eyeSmart EMR) by uniformly trained ophthalmic personnel using a standardized template and supervised by an ophthalmologist.[5]

### Cases

A total of 2,408,819 patients of all ages presented to the tertiary and secondary centers of the network during the study period. The standard protocol of managing a case of conjunctivitis in the network involves a high degree of suspicion for other differentials like microsporidial keratitis that is identified on clinical examination by raised epithelial lesions that are more prominent with fluorescein staining. These cases undergo epithelial scraping for microbiological evaluation.[6] The eyeSmart EMR was initially screened for patients with: (i) complaints of sudden onset of redness, irritation, discharge, swelling, or watering in the eye (ii) conjunctival findings of follicles/papillae, petechial hemorrhages, or pseudo-membrane (iii) corneal findings of subepithelial infiltrates (iv) final diagnosis of EKC in one or both eyes. The 21,196 patients identified with the search strategy were labeled as cases. 1,635 patients with acute presentation (≤1 week) from the district of Hyderabad from the above cohort were included for the trend analysis with the meteorological parameters.

### Data retrieval and processing

The data of 1,635 patients included in this study were retrieved from the electronic medical record database and segregated in a single excel sheet. The columns included the data on demographics, clinical presentation, and ocular diagnosis and were exported for analysis. The excel sheet with the required data was then used for analysis using the appropriate statistical software. Standardized definitions were used for occupation and socioeconomic status.[7] The geographic categorization of the districts of India was performed under the National Sample Survey Organization (NSSO) which defines "rural" as an area with a population density of up to 400 per km$^2$.[8] The Constitution (seventy-fourth Amendment) Act, 1992 defines a metropolitan area in India as, an area having a population of one million or more, comprised in one or more districts and consisting of two or more municipalities or panchayats or other contiguous areas, specified by the Governor by public notification to be a metropolitan area. The remaining districts were classified as urban.[9] The weather parameters of 33 districts of the state of Telangana were obtained from the Telangana State Development and Planning Society (TSDPS), Government of Telangana. TSDPS facilitates data collection through 1044 Automated Weather Stations (AWS), 64 global radiation sensors, and 41 soil moisture sensors across the state of Telangana to acquire data on a real-time basis. The AWS measures 6 weather parameters, namely, rainfall, wind speed, wind direction, pressure, humidity, and temperature in addition to Global Radiation and Soil Moisture at desired locations at every 1 h interval and transmits it in the form of SMS using GSM technology. At least, one AWS for each Mandal is installed in a grid of 10 km × 10 km.[10] The weather parameters were then mapped to the cohort of patients from the district of Hyderabad.

### Statistical analysis

Descriptive statistics using mean ± standard deviation and median with interquartile range (IQR) were used to elucidate the demographic data. Prevalence was calculated by dividing the number of EKC cases by the total number of patients presenting to the network from the given geographic location during the study period. The Medcal software (version 19.2.0) was used to perform Pearson's correlation coefficient analysis between the prevalence and individual weather parameters. The r-square ($r^2$) value of 0.12 or below indicates low, between 0.13 and 0.25 values indicate medium, 0.26 or above values indicate high effect size.[11]

## Results

### Demographics

Among the 21,196 patients (0.87%) with EKC, 19,203 reported acute (≤1 week) onset of the symptoms (90.6%). Among those with the acute presentation, the cohort from the district of Hyderabad included 1,635 (8.51%) patients. The mean age of the patients with EKC was 33.58 ± 17.74 years while the median age was 32 (IQR: 22–46) years. There were 13,095 (61.78%) male and 8,101 (38.22%) female patients with EKC. There were 9,829 (46.37%) patients with EKC from urban districts, 9,175 (43.29%) from rural districts and 2,192 (10.34%) from metropolitan regions.

### Hyderabad district cohort

Of the 182,789 patients who presented from the district of Hyderabad during the study period, 1,635 (0.89%) patients had an acute (≤1 week) onset of the symptoms. The mean age of the patients with EKC was 32.11 ± 17.12 years while the median age was 30 (IQR: 23–41) years. There were 963 (58.9%) male and 672 (41.1%) female patients with EKC. The highest prevalence was seen in April with 1.09% (167/15,313; 95% CI: 0.009 to 0.013) and the lowest was seen in July with 0.74% (118/16,039; 95% CI 0.006 to 0.009). The weather parameters of rainfall, temperature, humidity, and wind speed were assessed on a monthly interval. The month-wise distribution of the prevalence of acute cases of EKC from the district of Hyderabad is shown in Fig. 1.

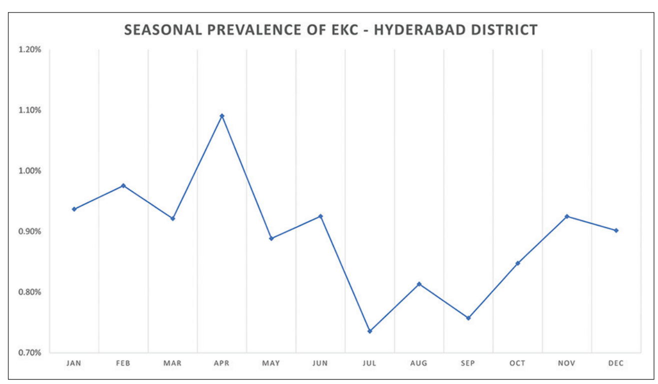


**Figure 1:** Seasonal variation of epidemic keratoconjunctivitis (EKC) in the district of Hyderabad. The prevalence of EKC increased steadily from November during winter to peak in April before decreasing with the onset of Monsoon

### Rainfall

The month-wise rainfall distribution is shown in Fig. 2a. the average rainfall from 2016–2019 was 2.08 mm/day. The highest rainfall was seen in September (6.25 ± 14.49 mm/day) and the lowest in February (0.01 ± 0.11 mm/day). The month-wise prevalence of EKC was negatively correlated with the distribution of rainfall (r = -0.6894), and this correlation was statistically significant ($r^2$ = 0.47/$P$ = 0.0131).

### Humidity

The month-wise relative humidity distribution is shown in Fig. 2b. The average relative humidity from 2016–2019 was 57.63%. The highest relative humidity was seen in September (74.79 ± 9.09%) and the lowest in April (42.05 ± 14.55%). The month-wise prevalence of EKC was negatively correlated with the distribution of humidity (r = - 0.8111), and this correlation was statistically significant ($r^2$ = 0.65/$P$ = 0.0014).

### Temperature

The month-wise temperature distribution is shown in Fig. 2c. the average temperature from 2016–2019 was 28.5°C. The highest average temperature was seen in May (34.16 ± 5.62°C) and the lowest in December (24.24 ± 3.83°C). The month-wise prevalence of EKC was not correlated with the distribution of temperature (r = 0.2793), and this correlation was not statistically significant ($r^2$ = 0.08/$P$ = 0.3793).

### Wind speed

The month-wise wind speed distribution is shown in Fig. 2d. the average windspeed from 2016–2019 was 7.28 km/h. The highest wind speed was seen in August (9.23 ± 4.7 km/h) and the lowest in January (5.06 ± 3.47 km/h). The month-wise prevalence of EKC was negatively correlated with the distribution of wind speed (r = -0.7535), and this correlation was statistically significant ($r^2$ = 0.56/$P$ = 0.0047).

## Discussion

This study sought to describe the correlation between the temporal pattern of presentation of acute EKC of presumed adenoviral etiology with meteorological parameters such as environmental temperature, rainfall, humidity, and wind speed in a cohort of patients presenting to a multitier hospital network in India using electronic medical records-driven analytics. The findings of this study suggest that there is a complex interplay of environmental factors with the temporal pattern of EKC in the population of the district of Hyderabad with a peak prevalence seen in April and the lowest seen in July. An increase in rainfall, wind speed, and humidity contributes to a lower prevalence of EKC cases during the year, whereas surprisingly temperature did not have any bearing in the prevalence of EKC in the population. Therefore the findings of this study suggest that unlike popular perception, higher temperatures, or the onset of summer alone might not have a detrimental effect on the spread of viral epidemics. This information may have broader implications particularly in the context of viral outbreaks.

Lee *et al.*[12] reported a seasonal variation of adenoviral conjunctivitis in a total of 926 patients over 30 years in the United States. The seasonal trend was analyzed in four quarters in a year and the number of cases was highest in the months from July to September and lowest from April to June contrary to the findings in our study. The seasonal variation

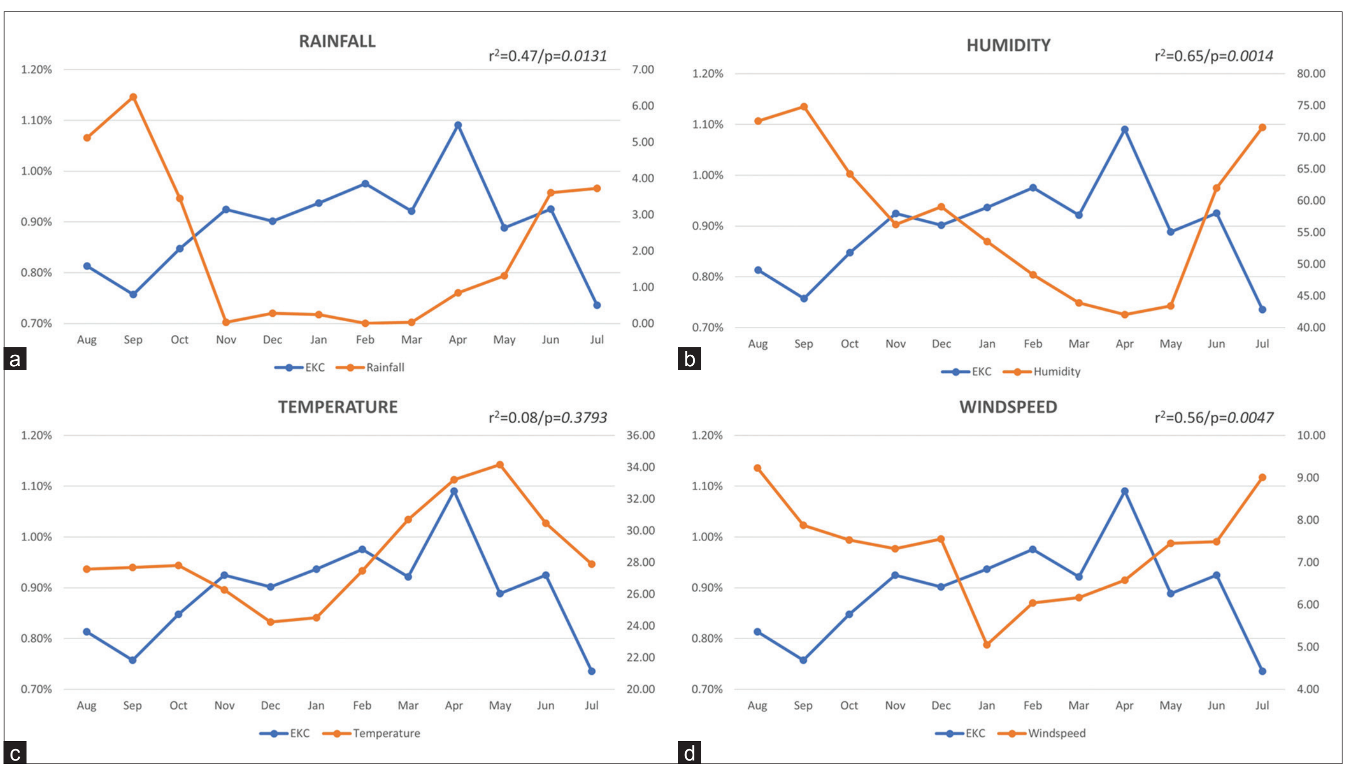


**Figure 2:** Monthly variation of environmental factors and the prevalence of epidemic keratoconjunctivitis (EKC) in the district of Hyderabad. The month-wise prevalence of EKC was negatively correlated with the distribution of rainfall (a, r = -0.6894), humidity (b, r = -0.8111), and wind speed (d, r = -0.7535) but not with temperature (c, r = 0.2793)

accounts for the disparity in months but the peak cases were seen in summer in both the geographies. In our study, the peak prevalence was noted in April which is in the peak of summer. This study lacked epidemiological information such as gender, age, and geography which are the strengths of our cohort and reported in our study.

Zhang *et al*.[3] analyzed the virology and epidemiology of global adenovirus-associated conjunctivitis outbreaks from 1953–2013 globally. The epidemiological findings suggested that EKC and acute hemorrhagic conjunctivitis (AHC) were circulating predominantly in Asia during the early winter and spring, which is similar to our current study with the steady increase in prevalence from November to April. Of the 12 AHC outbreaks studied, there was one from southeast Asia from 1970–71 that occurred in May in 253 patients of the ages between 3–65 years. The study also concluded that EKC, AHC, and PCF outbreaks have different circulating patterns throughout the world and are caused by different adenovirus serotypes notably Ad8, Ad7, and Ad2 coinfection with enterovirus 70 (EV70).

Aoki *et al*.[13] described 21-year surveillance of adenoviral conjunctivitis in Sapporo, Japan. The occurrence of infection is more frequent in the summer season for the viral genotypes of Ad3, Ad4, and Ad37. Summer in Japan temporally lasts from June to August and the weather conditions are hot and humid, with temperatures that can range as high as 35°C.[14]

Wang *et al*.[15] in a recent analysis from 100 Chinese cities with more than 40 cases of COVID-19 reported that 1°C increase in temperature and 1% increase in relative humidity lower R (daily effective reproductive number) by 0.0383 and 0.0224, respectively. Using the daily R values from January 21 to 23, 2020 as proxies of non-intervened transmission intensity, they found under a linear regression framework for 100 Chinese cities that high temperature and high relative humidity significantly reduce the transmission of COVID-19. This association highlights the importance of such surveillance during viral outbreaks. The negative correlation with humidity and prevalence of cases is strikingly similar in both the viruses, though there was no statistically significant correlation with temperature in our study. The aim of this study is not to draw a direct comparison between the temporal pattern of EKC and the ongoing COVID-19 outbreak globally but to explore similarities among them. The two viruses of adenovirus (dsDNA) and coronavirus (ssRNA) are distinct and the fatality rate is significant in the latter and therapeutic information is evolving with each day.[16]

To our knowledge, this is the first paper in India to describe the seasonal variation of EKC along with the correlation with meteorological parameters of rainfall, humidity, wind speed, and temperature. This new knowledge will sensitize people to understand the prevalence pattern of EKC and guide on expectations during potential outbreaks in the population with local relevance to geography.

The greatest strengths of this study were its high statistical power due to its large sample size and its utilization of completely digital data entry and extraction methods. The principal limitation of the study was its hospital-based method of selection of subjects which may have introduced a certain level of ascertainment bias and lack of molecular data of viral genotypes. We also have not considered the varying pattern of different viral strains with regards to yearly trends and their relation to weather. This limitation underlies the importance of having registries to identify new cases to ensure faster response and an understanding of the behavior of these viral epidemics at a larger scale in our nation. The establishment of a global adenovirus surveillance system that includes epidemiological and virological surveillance has been advocated to track the pattern of outbreaks in countries around the world.[4] Patients who are diagnosed with conjunctivitis of presumed adenoviral etiology must be investigated further for the type of viral strain and the information passed on to a nodal agency to help identify the type and pattern of the outbreaks in the population. The current study may not account for all the cases in the given geography due to the presentation bias to the hospital but lends insight into the existing pattern of the prevalence of EKC in the population to promote the prevention of disease and limit the spread of the same.

## Conclusion

In conclusion, this study aimed to describe the correlation between the temporal pattern of presentation of acute EKC of presumed adenoviral etiology with meteorological parameters such as environmental temperature, rainfall, humidity, and wind speed in a cohort of patients from the district of Hyderabad presenting to a multitier ophthalmology hospital network in India. The findings show that an increase in rainfall, wind speed, and humidity contributes to a lower prevalence of EKC cases during the year and no statistically significant correlation with temperature was found. This is contrary to the popular perception of higher temperatures leading to lower risk of transmission of contagious viral infections and highlights the importance of regular surveillance for better preparedness in the event of viral outbreaks from a public health perspective.

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### Author contributions

The corresponding author states that authorship credit of this manuscript was based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. All listed authors met conditions 1, 2, and 3. All persons designated as authors qualify for authorship, and all those who qualify are listed. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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