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Short communication



Outpatient human coronavirus associated conjunctivitis in India

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ABSTRACT

Background: Viral conjunctivitis (pink eye) can be highly contagious and is of public health importance. There remains significant debate whether SARS-CoV-2 can present as a primary conjunctivitis. The aim of this study was to identify pathogens associated with outpatient infectious conjunctivitis during the COVID-19 Delta surge. **Methods:** This prospective study was conducted in the spring and summer months of 2021. 106 patients with acute conjunctivitis who presented to the Aravind Eye Center in Madurai, India were included. One anterior nasal swab and one conjunctival swab of each eye were obtained for each enrolled patient. Samples were subsequently processed for unbiased metagenomic RNA deep sequencing (RNA-seq). Outcomes included clinical findings and codetection of other pathogens with SARS-CoV-2 in patients with conjunctivitis.

Results: Among the 13 patients identified with human coronavirus RNA fragments in their swabs, 6 patients had SARS-CoV-2 infection, 5 patients had coinfections of SARS-CoV-2 and human adenovirus (HAdV), 1 patient had a coinfection with human coronavirus OC43 and HAdV, and 1 patient had a coinfection of *Vittaforma corneae* and SARS-CoV-2. 30% had bilateral disease and symptoms on presentation. Petechial hemorrhage was noted in 33% of patients with SARS-CoV-2 infection. No patients with SARS-CoV-2 or SARS-CoV-2 and HAdV infections had subepithelial infiltrates on presentation. All patients denied systemic symptoms.

Conclusions: Among the patients presented with conjunctivitis associated with human coronavirus infection, over 50% of the patients had co-infections with other circulating pathogens, suggesting the public-health importance of broad pathogen testing and surveillance in the outpatient conjunctivitis population.

1. Introduction

SARS-CoV-2 RNA has been detected in the conjunctiva and tears of patients hospitalized with moderate to severe COVID-19 disease [1,2]. Conjunctivitis associated with COVID-19 disease is documented in both the outpatient and hospitalized populations, although the prevalence varies dependent on the study and population investigated and it remains a debate whether infection with SARS-CoV-2 can present as a primary conjunctivitis [1,3-6].

In a companion paper, we presented a study in which we used

unbiased metagenomic sequencing to identify pathogens known to cause conjunctivitis during the conjunctivitis season that happened to coincide with the Delta surge in India. We found that HAdV was the most common pathogen detected in patients who presented to the Aravind Eye Hospital [7]. Because all patients were subjected to unbiased testing, we were able to detect other viruses and pathogens that may have not been on the differential. In this paper, we describe a subgroup of those patients who were positive for human coronavirus (HCoV) RNA in either conjunctival or anterior nasal samples collected on presentation. Cases of presumed co-infections are also characterized. This

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information may assist outpatient management given that SARS-CoV-2 will likely be endemic in the setting of other known circulating pathogens causing conjunctivitis.

2. Materials & methods

Ethical approval was obtained from the Aravind Eye Hospital and University of California San Francisco (UCSF) Institutional Review Boards (IRB). The Stanford University IRB waived review. This study adhered to the tenets of the Declaration of Helsinki. All patients with presumed infectious conjunctivitis at the Aravind Eye Clinic in Madurai, India, from April 1 to May 1, 2021 and from June 1 to September 17, 2021, were included in the analysis. The gap in sample collection represented a lockdown period in which all research activities at Aravind were suspended due to the Delta surge. A conjunctival swab of each eye and an anterior nasal swab of both nares were obtained for each enrolled patient. Swabs were placed in DNA/RNA Shield (Zymo Research, Irvine, CA) and stored at -80°C until processing. Samples were deidentified and all laboratory personnel were masked. RNA sequencing was performed as previously described [8]. Briefly, 5 μL of extracted RNA of each sample was converted to cDNA and sequencing libraries were prepared using the NEBNext ULTRA II RNA Library Prep Kit for Illumina (New England Biolabs, Ipswich, MA) according to manufacturer's instructions and then pooled and sequenced on the NovaSeq system (NovaSeq 6000, Illumina, San Diego, CA) using 150-nucleotide paired-end sequencing.

Analysis of the sequenced data to identify pathogens was performed as described [8]. The pre-specified criteria for positive pathogen are 1) it is known to be a human pathogen and represent the most abundant

reads after water background subtraction or 2) two or more unique reads covering separate regions in DNA virus genomes or 3) one or more unique reads matching RNA virus genomes. SARS-CoV-2 positive samples on RNA-seq were subjected to a laboratory-developed confirmatory SARS-CoV-2 reverse transcription-quantitative PCR (RT-qPCR) at the Stanford Clinical Virology Laboratory [9]. Testing was performed as previously described, except that RNA was extracted using the Quick-DNA/RNA Microprep Kit (Zymo Research, Irvine, CA) and eluted in 20 μL of DNase/RNase free H_2O . This multiplex RT-PCR targets the SARS-CoV-2 *envelope* (*E*) gene and also includes detection of human RNase P nucleic acids as internal control in a separate fluorescence channel. The presence of RNase P at a cycle threshold (Ct) value less than 35 cycles indicates adequate specimen collection and nucleic acid extraction, as well as the absence of RT-PCR inhibitors. Samples that were positive on confirmatory RT-qPCR underwent a genotyping RT-qPCR as previously described [10,11]. Genotyping was performed using a laboratory-developed two-reaction multiplex RT-qPCR assay targeting spike gene mutations L452R, E484K, and N501Y in reaction 1 and del69–70, K417N, and T478K in reaction 2 [11].

3. Results

A total of 318 conjunctival and anterior nasal swab samples from 106 patients were included in the study. The sequencing depth, host reads, and non-host reads for all samples are shown in Fig. 1. Of those, 13 patients had at least one sample that was positive for human coronavirus (OC43 and SARS-CoV-2) RNA on RNA-seq (Table 1 and Fig. 2). Patient demographics and clinical signs and symptoms on presentation are shown in Table 1. The mean age was 40 years old and 77% were male.

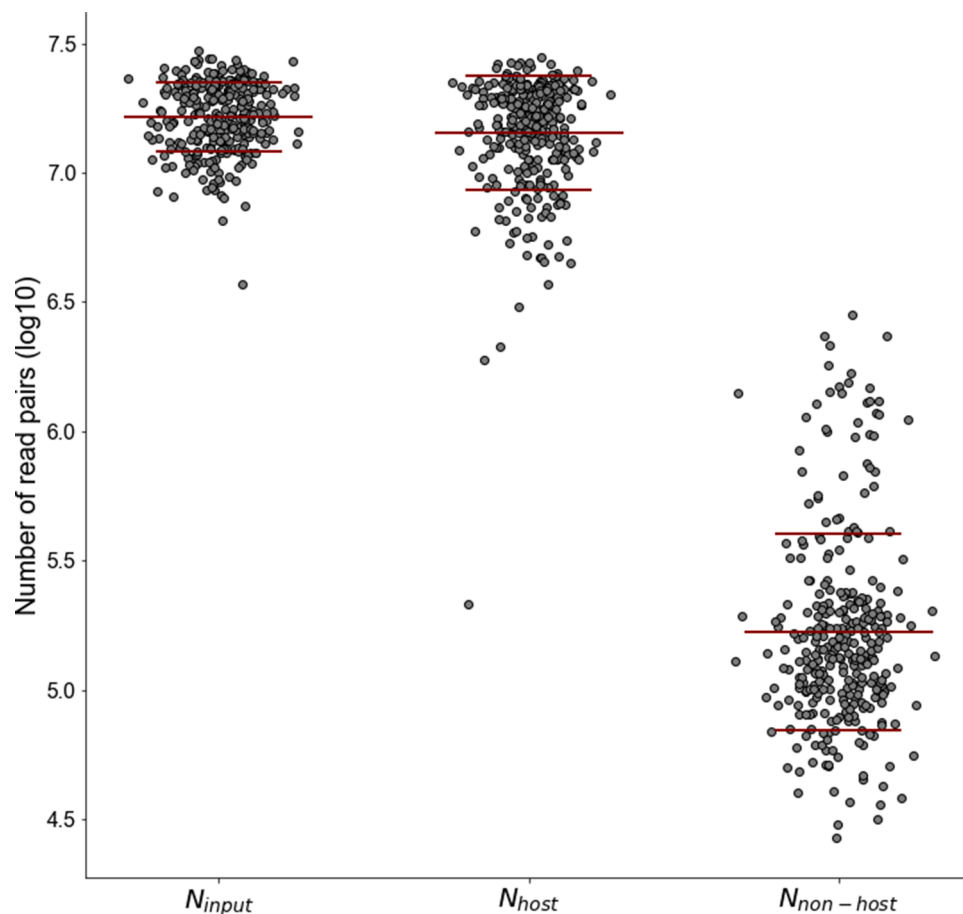


Fig. 1. Characteristics of metagenomic RNA deep sequencing. Number of sequencing read counts as a function of total, host, and non-host for 318 samples. Each dot represents a sample. Bars represent mean and standard deviation.

Table 1
Patient demographics and clinical signs and symptoms on presentation for 13 coronavirus-positive patients with conjunctivitis. Only patient # 7 had documented subepithelial infiltrates and membrane or pseudomembranes. Abbreviations: HAdV, human adenovirus; HCoV-OC43, human coronavirus OC43; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MDS, metagenomic RNA deep sequencing.

Pt #	Age (years)	Sex	Contact affected	Symptom Duration (days)	Eye (s) with conjunctivitis	Sore Throat	Runny Nose	Pre-auricular lymphadenopathy	Itching	Tearing	Purulent Discharge	Petechiae	MDS Right Conjunctiva	MDS Left Conjunctiva	MDS Nose
1	22	M	No	1	Right	No	No	No	Yes	Yes	Yes	Yes	SARS-CoV-2	Negative	SARS-CoV-2
2	50	M	Unknown	1	Left	No	No	No	Yes	Yes	Yes	Yes	SARS-CoV-2	SARS-CoV-2	SARS-CoV-2
3	25	M	No	2	Right	No	No	No	No	Yes	Yes	No	SARS-CoV-2	Negative	HAdV
4	21	M	Yes	2	Left	No	No	No	No	No	Yes	No	Negative	<i>Vittaforma corneae</i> , SARS-CoV-2	Negative
5	63	M	No	1	Left	No	No	No	No	Yes	Yes	No	Negative	SARS-CoV-2	SARS-CoV-2
6	22	F	No	6	Left	No	No	Left	Yes	Yes	No	No	Negative	SARS-CoV-2	Negative
7	60	M	No	3	Left	No	Yes	Left	No	Yes	No	No	Negative	HAdV	HCoV-OC43, HAdV
8	39	M	No	1	Right	Yes	No	No	No	No	Yes	Yes	SARS-CoV-2	Negative	SARS-CoV-2
9	24	M	No	10	Both	No	No	Left	Yes	Yes	Yes	No	SARS-CoV-2, HAdV	HAdV	HAdV
10	52	M	No	6	Both	No	No	Right	Yes	Yes	No	No	SARS-CoV-2	SARS-CoV-2	HAdV
11	40	M	No	5	Left	No	No	No	Yes	Yes	Yes	No	Negative	Negative	SARS-CoV-2
12	65	F	No	6	Both	No	Yes	Right	Yes	Yes	Yes	No	HAdV	SARS-CoV-2, HAdV	HAdV
13	34	F	No	5	Both	No	No	No	No	No	No	Yes	HAdV	HAdV	SARS-CoV-2, HAdV

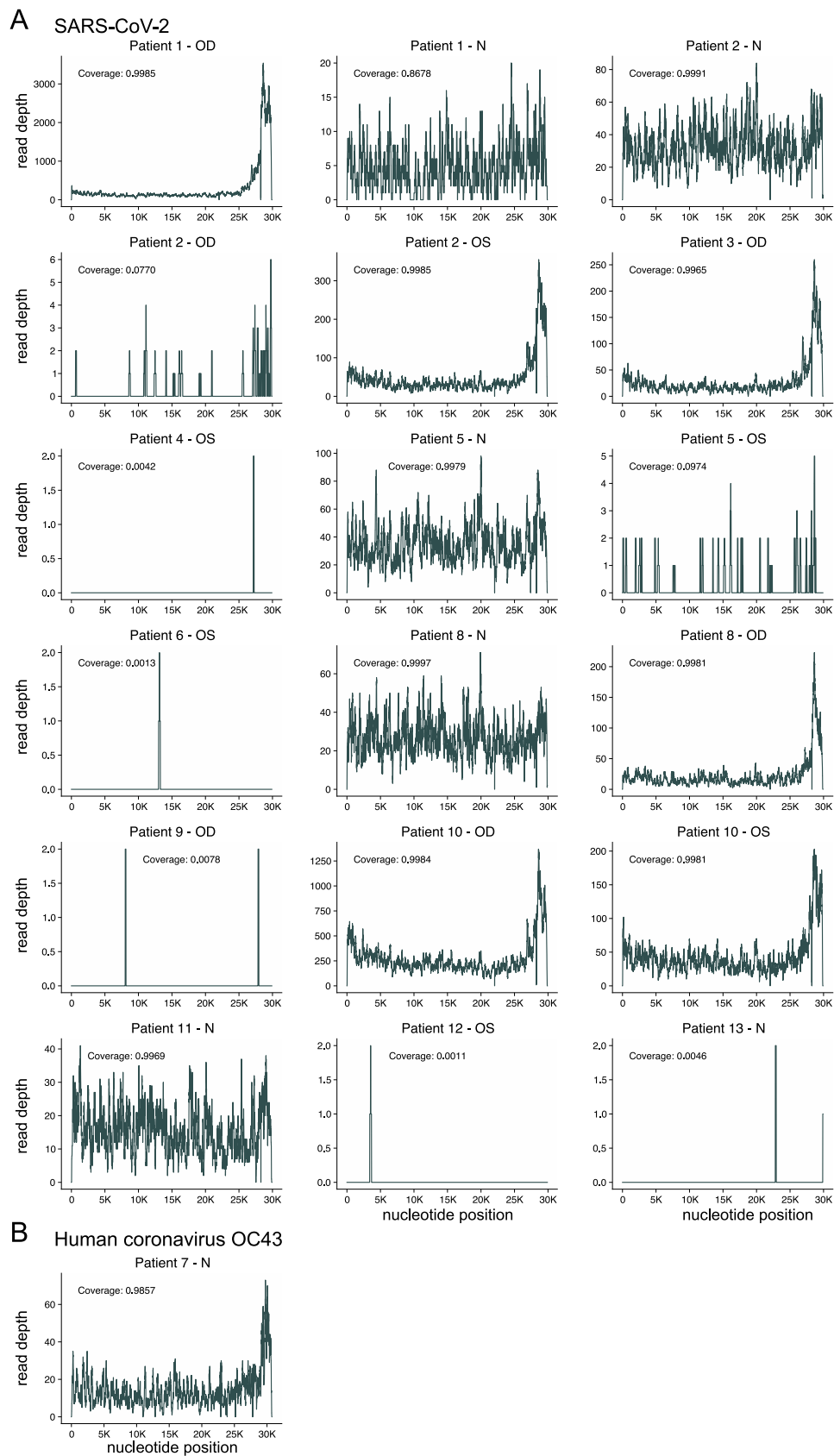


Fig. 2. Identification of human coronaviruses by metagenomic RNA deep sequencing. A. Alignment of detected SARS-CoV-2 sequencing reads to the SARS-CoV-2 genome (NCBI reference sequence NC_045512) for each positive sample. B. Alignment of detected human coronavirus OC43 reads in the nasal sample of patient #7 to the NCBI reference sequence NC_006213.1. Abbreviations: OD, right eye; OS, left eye; N, nasal.

69% (95% confidence interval (CI): 42% to 87%) of the patients had unilateral disease. Of the symptoms queried, the most common symptom was tearing (77%, 95%CI: 50% to 92%). Other symptoms included itchiness (46%, 95%CI: 23% to 71%), runny nose (15%, 95%CI: 3% to 42%), and sore throat (8%, 95%CI: 0% to 33%). No patients reported coughing (0%, 95%CI: 0% to 23%) or diarrhea (0%, 95%CI: 0% to 23%). The most common clinical sign was purulent discharge (69%, 95%CI: 42% to 87%). Other signs included pre-auricular lymphadenopathy (38%, 95%CI: 18% to 64%), conjunctival petechiae (31%, 95%CI: 13% to 58%), subepithelial infiltrates (8%, 95%CI: 0% to 33%), and membranes or pseudomembranes (8%, 95%CI: 0% to 33%).

The Delta surge in the Tamil region began in March, peaked in May, and quickly tapered off by July 2021 (Fig. 3). This period coincided with the conjunctivitis season in India [12]. The presence of SARS-CoV-2 and HAdV RNA in either conjunctival or nasal samples was presumed to be pathologic as these viruses are not considered normal flora of the conjunctiva or respiratory tract. Six patients had only SARS-CoV-2 RNA detected and another five patients had co-detection of SARS-CoV-2 and HAdV RNA. One 60-year-old male patient with left eye involvement had HAdV RNA detected in the conjunctival swab of his left eye and HAdV and human coronavirus OC43 RNA detected in his nasal swab. A conjunctival swab from the left eye of a patient with unilateral conjunctivitis of the left eye was positive for *Vittaforma corneae* and SARS-CoV-2. Thus, of the 106 patients with presumed acute infectious conjunctivitis evaluated, 11% (95%CI: 7% to 19%) had SARS-CoV-2 associated conjunctivitis and 7% (95%CI: 4% to 14%) had co-infections with HAdV, SARS-CoV-2, or *Vittaforma corneae*. Representative external photos for each infectious category are shown in Fig. 4.

Fifty eight percent (7/12) of patients with detectable SARS-CoV-2 by RNA-seq were confirmed by RT-qPCR and genotyping demonstrated the Delta variant. The 5 patients not detectable by RT-qPCR had limited

numbers of reads via sequencing.

4. Discussion

Unbiased pathogen detection using RNA-seq of conjunctival and anterior nasal samples of patients with acute conjunctivitis during the Delta variant surge in southern India showed not only the association of SARS-CoV-2 infection and outpatient conjunctivitis, but also the co-infections of other circulating viruses.

Most patients with SARS-CoV-2 infection or co-infection with HAdV presented with tearing and purulent discharge. Exam findings were notable for conjunctival petechial hemorrhages in 31% of patients. Subepithelial infiltrates and pseudomembranes presented in only one patient whose samples had codetection of HAdV and the human coronavirus OC43 RNA and were not present in any SARS-CoV-2 positive patients. Human coronavirus OC43 is a common HCoV that can cause respiratory symptoms, gastroenteritis, and conjunctivitis [13]. From a public health standpoint, the co-circulation of HAdV, HCoV-OC43, and SARS-CoV-2 suggests the importance of broad pathogen surveillance, particularly in the outpatient setting, where paradoxically, testing is rarely performed.

It was notable that none of the patients who presented to the Aravind Eye Center had a known diagnosis of SARS-CoV-2 infection. While 2 out of 13 patients (15%) positive for human coronaviruses had rhinorrhea, none of these patients reported other respiratory symptoms or GI symptoms. While it appeared that these participants sought medical care solely for conjunctivitis, one cannot rule out under-reporting given the perceived stigma associated with potential SARS-CoV-2 infection during this time period. Thus, as we continue to adapt to the continual presence of SARS-CoV-2, it may be prudent for the clinical staff to adhere to personal protective equipment protocols when examining conjunctivitis patients.

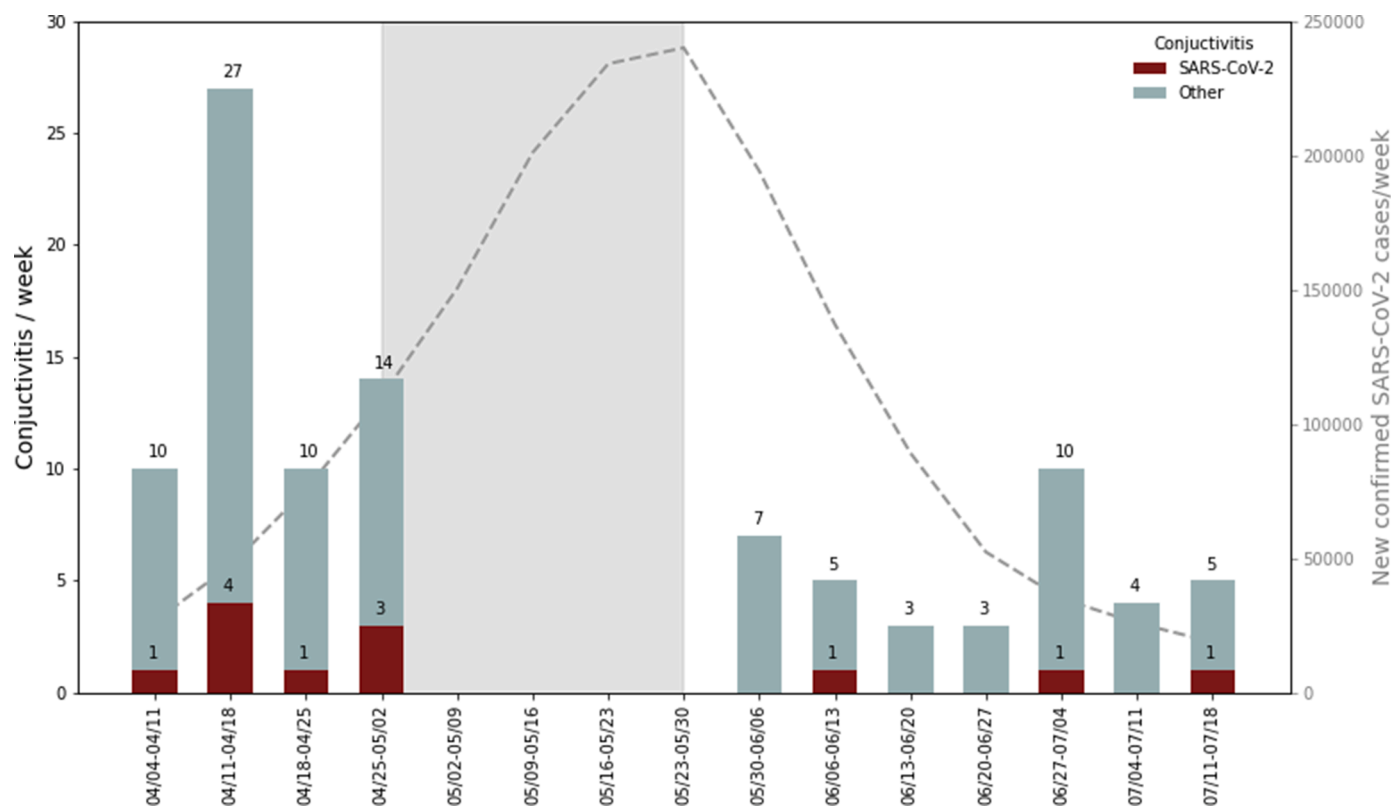


Fig. 3. Cases of human coronavirus-associated conjunctivitis during the Delta coronavirus variant surge at the Aravind Eye Center in southern India. Stacked bar graph of conjunctivitis cases enrolled in the study. Solid gray bar represents the stoppage of clinical activities at the Aravind Eye Center. Dotted gray line represents the new confirmed SARS-CoV-2 cases in the population in the Tamil region of India.

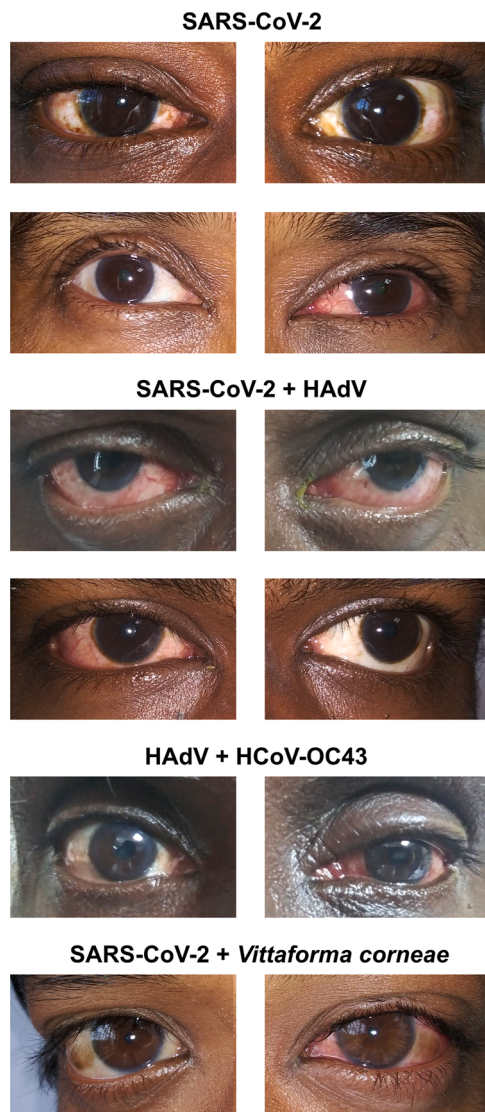


Fig. 4. Representative external ocular photos of patients with human coronavirus infections. Each row of images represents the right and left eyes of a unique patient. Abbreviations: HAdV, human adenovirus; HCoV-OC43, human coronavirus OC43; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

5. Limitations

A limitation of this study is the lack of long-term follow-up. It was unclear if any of these patients subsequently developed respiratory symptoms or had a poor visual outcome. However, previous studies have shown that most SARS-CoV-2 associated outpatient conjunctivitis cases appeared mild [1] and the majority of patients' symptoms resolved within 3 weeks [5]. Similar to many places around the world, clinical studies were placed on hold during the surge, as was the case at the Aravind Eye Center. Thus, we were unable to determine the true prevalence of SARS-CoV-2 associated conjunctivitis during the Delta surge in the region. This limitation resulted in the small sample size and is reflected in the large confidence intervals for the findings described in this study.

6. Conclusions

Conjunctivitis may be the only presenting clinical sign of patients with SARS-CoV-2 infection. Co-infections with other DNA viruses or

fungi may occur, indicating a need for the surveillance of outpatient conjunctivitis cases and the consideration of broad pathogen testing.

Nonauthor contribution

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