

Review

There is a Role in Detection of SARS-CoV-2 in Conjunctiva and Tears: a comprehensive review.

Federico Bernabei¹, Piera Versura¹, Giada Rossini², Maria Carla Re²

¹DIMES - UO Oftalmologia – Laboratorio Analisi Superficie Oculare e Ricerca Traslazionale Alma Mater Studiorum Università di Bologna e AOU di Bologna Policlinico di S. Orsola

²DIMES - UO Microbiologia -Alma Mater Studiorum Università di Bologna e AOU di Bologna Policlinico di S. Orsola

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SUMMARY

Data on the involvement of the ocular surface and its relationship with Coronavirus disease 2019 (COVID-19) are still minimal and not univocal.

The respiratory tract is the structure most affected by COVID-19, and the serious form of the disease is characterized by severe pneumonia, acute respiratory distress syndrome and hypercoagulation. However, accumulating evidence shows that other organs could be reached by the virus, thus causing further comorbidities. To date, the exact route / routes of transmission of COVID-19 are still unclear. The respiratory tract is probably not the only route of transmission for this viral infection and some authors have also speculated that COVID-19 droplets, or infected hands, could contaminate the conjunctiva, which could therefore represent the initial site of an infection spread.

Theoretically, the role of the ocular surface, a biological site still relatively unexplored, appears scientifically relevant in understanding the Severe Acute Respiratory Syndrome - Coronavirus – 2 (SARS-CoV-2) infection. The purpose of this paper is to summarize the current literature in order to elucidate the potential role of tear and conjunctival sampling to detect SARS-CoV-2 for the diagnosis of COVID-19 and to monitor patients during follow-up.

Key Words: COVID-19; SARS-CoV-2; Conjunctiva; Tears.

Corresponding Author: Piera Versura, BSD

Ophthalmology Unit, DIMES University of Bologna, S.Orsola-Malpighi Hospital, Pad. 1 Palagi, Via Palagi, 9 40138 Bologna.

Phone: +39 051 2142850; Fax: +39 051 6362846; E-mail: piera.versura@unibo.it

INTRODUCTION

Severe Acute Respiratory Syndrome-Corona-Virus-2 is a novel lineage in the phylogenetic tree of beta-coronaviruses. It displays 89% nucleotide identity with bat SARS-like CoVZXC21 and 82% with that of human SARS-CoV (Chan et al., 2020). The spike proteins of SARS-CoV-2 associated with the host receptor angiotensin-converting enzyme 2 (ACE2) in target cells of sensitive tissues can result in infection. The mammalian serine protease Transmembrane Serine Protease 2 (TMPRSS2) or the protease Furin (also known as Paired basic Amino acid Cleaving Enzyme) appear to trigger the spike protein for interaction with ACE2 (Hoffmann et al., 2020, Zhou et al., 2020).

ACE2 is also the receptor for SARS-CoV; both types of virus have high human-to-human transmissibility and can cause severe acute respiratory disease (Benvenuto et al., 2020).

Viral diagnosis plays an essential role in the control of any communicable disease, and this has been unequivocally shown in the recent global pandemic caused by SARS-CoV-2, also known as Coronavirus disease 2019 (COVID-19) (Li & Ma, 2020). Real-time reverse transcriptase polymerase chain reaction-based assays (RT-PCR) for detecting SARS-CoV-2 performed on respiratory specimens are the current reference standard for COVID-19 diagnosis. To limit the spread of infection, these assays are also used to track affected but asymptomatic patients, according to proposed guidelines that also consider sustainability of the flow.

Biological samples other than those from the respiratory tract, such as feces (Chen et al., 2020c), saliva (Lm et al., 2020, Williams et al., 2020), urine (Peng et al., 2020), and semen (Paoli et al., 2020) have been investigated.

On the other hand, data published on the involvement of the ocular surface, in particular the conjunctival mucosa and the corneal epithelium, are still minimal and inconsistent.

Interestingly, SARS-CoV-2 has also been identified in tears, as was SARS-CoV in 2003 (Karimi et al., 2020, Loon et al., 2004, Xia et al., 2020). The expression of ACE2 and TMPRSS2 has been identified in several tissues in the human body (such as lung alveolar mucosa, oral mucosa, gastrointestinal duct, kidney), including the cornea and conjunctiva (Lange et al., 2020, Ma et al., 2020), where they are both co-expressed (Sungnak et al., 2020). These findings suggest that these tissues could be possible sites of original infection and potential reservoirs for diffusion (Sun et al., 2020).

Although the expression level of ACE2 on the conjunctiva appears to be lower than that in the lung, at least in mice, (Zhang et al., 2020) it could be a potential infection route of SARS-CoV-2 via the ocular surface. A comparison of SARS-CoV-2, SARS-CoV and MERS (Middle East

respiratory syndrome)-CoV receptors on the ocular surface and in the lung is given in a recent review work by Willcox and collaborators (Willcox et al., 2020). The diagnostic role of the conjunctival swab in investigating the local involvement of the ocular surface by SARS-CoV-2 has been reported in few studies and on a very limited number of patients, often occasional observations on a single patient (Chen et al., 2020b, Colavita et al., 2020, Xia et al., 2020, Zhang et al., 2020). In particular, the conjunctival swab test was found positive for SARS-CoV-2 in only about 2.5-5% of patients, according to studies conducted in the Wuhan region (Wu et al., 2020, Zhou et al., 2020). It is worth noting that the positivity of eye swabs persists over time compared with nasopharyngeal swabs. In particular, conjunctival swab positivity can be detected for over two weeks after the negativity of the nose pharyngeal swab (Colavita et al., 2020, Hu et al., 2020).

THE OCULAR SURFACE AS A DEFENSIVE BARRIER TO PATHOGENS

The ocular surface system (Gipson 2007) includes the epithelia of the cornea, the conjunctiva, the corneo-scleral limbus with stem cells, lacrimal, accessory, and meibomian glands, tears, the eyelashes with their associated glands, and the nasolacrimal duct. All the various components of this system are integrated by the nervous, endocrine, vascular, and immune systems to provide a refractive smooth surface of the cornea and a primary defensive wall to environmental irritants, allergens and pathogens.

All the epithelia of the ocular surface are continuous, from the lacrimal glandular epithelium to the ductal epithelium of the nasolacrimal system, and share functional properties with the mucus membranes of the respiratory tracts (Knop & Knop, 2007, Paulsen, 2008). However, the need to maintain optical properties is crucial at the ocular surface and make it a unique mucosal immune lining. In fact, to effectively counteract microbial diseases without leading to impaired corneal transparency, the immune response must be precisely modulated through the recruitment of competent immune cells (Akpek & Gottsch, 2003, Foulsham et al., 2018, Galletti, et al., 2017).

The corneal and conjunctival epithelial cells are sealed by adherent junctions that act as a physical barrier against the external environment, and lie above a connective tissue, looser in conjunctiva and highly organized and compact in the cornea. Both epithelium and stromal tissue present immunocompetent resident cells belonging to the immune defense system, including CD8+ T and CD4+ T cells, macrophages (CD68+), Langerhans cells expressing HLA-DR (Pflugfelder & de Paiva, 2017). The first line of defense of the ocular surface is the

presence of a healthy tear film that protects it from the external environment and provides an effective clearance and self-cleaning system under normal conditions.

Tears play a fundamental role in the innate defense against microorganisms (Garreis, et al., 2010, Maarouf et al., 2018, McDermott, 2013). Their antimicrobial function is exerted through three mechanisms: i) blinking and reflex tearing of the tear film, which results in flushing and washout of invading microorganisms; ii) inhibition and/or killing of microorganisms by several antimicrobial proteins (including lysozyme, lactoferrin, lipocalin, and secretory immunoglobulins A (IgA)); iii) entrapment of microorganisms by high-molecular weight glycoproteins (mucins, MUC), MUC2 and gel-forming MUC5Ac.

The lacrimal duct operates the passage of the virus from ocular to respiratory tract mucosa as it opens at the inferior meatus located underneath the inferior nasal turbinate. Transport may occur as a simple fluid exchange between sites through the conduit without onsite viral replication (Olofsson et al., 2005). However, the possibility of virus inoculation in nasolacrimal duct epithelial cells exists, as these cells both secrete and reabsorb tear fluid (Paulsen, 2003).

THE OCULAR SURFACE AS A PORTAL OF INFECTION

In addition to the respiratory tract mucosa, the ocular surface certainly represents a site in the human body which is similarly exposed to contaminated and infectious droplets (Konjevoda et al., 2020, Paulsen, 2008). Given the anatomical connection and immunological interdependence between the eye and the nose, the ocular surface may also be considered a portal to respiratory system infection. The ocular and respiratory tract mucosa share host cell receptors for several respiratory viruses, such as epithelial cell lectin-binding sites and, in particular, glycoproteins bearing terminal sialic acids (Kumlin et al. 2008).

Human respiratory viruses display a variable ocular tropism, which can cause ocular infection and further respiratory tract infection following the first contact with the eye (Figure 1) (Belser, et al., 2013). In fact, the virus is capable of either replicating in the ocular surface epithelial cells or simply draining with tears into the nasolacrimal duct and further infecting the respiratory tract if the innate immune system does not neutralize it earlier. The adenovirus and influenza virus can frequently cause epidemic, highly contagious, severe ocular diseases such as keratoconjunctivitis or conjunctivitis (Belser et al., 2013, Creager et al., 2018), and tropism in conjunctival cells has been demonstrated in *in vitro* models (Chan et al., 2010).

Previous studies have indicated that coronavirus infections in humans rarely associate with ocular complications, but suggest that ocular exposure may be a portal of entry for these viruses

and that contact with infected eyes could be one route of transmission. For instance, HCoVNH (New Haven coronavirus) positivity has been found in children affected by Kawasaki disease associated with bilateral conjunctivitis (Esper et al., 2005) but the etiology of the disease is still unclear. Kawasaki disease is an acute febrile systemic childhood vasculitis, which is suspected to be triggered by respiratory viral infections. Interestingly, peaks of severe Kawasaki-like disease have been described in association with the SARS-CoV-2 epidemic, suggesting that this could be a trigger for the disease and indicating the potential timing of an increase in incidence of the disease in COVID-19 epidemics (Ouldali et al., 2020).

In the SARS-associated coronavirus pneumonia identified in 2003, the virus was found to transmit via contact with mucous membranes, including those of the eyes (Peiris et al., 2003), as suggested by increased SARS transmission from infected patients to health care workers without eye protection (Raboud et al., 2010). Although the World Health Organization in 2003 included tears in the body fluids potentially containing SARS-CoV, the clinical impact is not yet clear ('WHO | Update 27 - One month into the global SARS outbreak' n.d.).

SARS-associated coronavirus was detected by Real Time Polymerase Chain Reaction (RT-PCR) in conjunctival samples from suspected patients without ocular symptoms (Loon et al., 2004), whereas conjunctival and tear samples from confirmed SARS patients, similarly without ocular symptoms or signs, tested negative (Chan et al., 2004, Yuen et al., 2004, Zhou et al., 2020).

The tropism of SARS-CoV2 to ocular surface cells remains controversial. In *in vitro* studies, SARS-CoV-2 replication was greater than SARS-CoV replication in conjunctival cells, but the release of pro-inflammatory cytokines was lower than in MERS-CoV and influenza virus H5N1 (Hui et al., 2020). A meta-analysis on six studies recently reported a very low pooled sensitivity of ocular tissue/fluid in detecting SARS-CoV-2 compared to samples from nasopharyngeal swabs (Ulhaq & Soraya, 2020). The prevalence of viral detection in infected patients is provided in the following section of this paper, where the literature was reviewed as of June 2, 2020.

OCULAR SURFACE AND COVID-19 INFECTION: REVIEW OF LITERATURE

An initial literature search was performed in several databases, including Web of Science, Ovid, Cochrane Database, and Scopus for original articles published up to August 2020. Keywords were used in combination, including: "COVID-19," "SARS-CoV-2," "coronavirus," "eye," "ocular," "conjunctival," "ocular surface," "ophthalmic," and "conjunctivitis." A second literature search was conducted by identifying relevant references

of initially included articles. The searches were conducted by two independent investigators (FB, PV). Any discrepancies were resolved by discussion or by input from the third reviewer (MCR).

Study Selection. After removing duplicate publications, 2 reviewers (FB, PV) independently screened the titles and abstracts of all identified citations. The full text of citations judged as potentially eligible were obtained and independently screened for eligibility, and any disagreement was resolved by discussion with the authors.

Eligibility Criteria. The articles were considered eligible if the studies met the following inclusion criteria: 1) study type: case series or reports 2) population: patients with COVID-19 who described ocular manifestations that were tested for SARS-CoV-2 in ocular secretions via various sampling or detection methods. We excluded studies that described ocular manifestations of COVID-19 but did not document testing for SARS-CoV-2 in ocular secretions.

A rapidly increasing number of studies has investigated ocular signs and symptoms in patients infected with SARS-CoV-2. (Chen et al., 2020a, Fang et al., 2020, Guan et al., 2020, Hong et al., 2020, Karimi et al., 2020, Liang & Wu, 2020, Mungmungpantipantip & Wiwanitkit, 2020, Seah et al., 2020, Wu et al., 2020, Xia et al., 2020, Xie et al., 2020, Zhang et al., 2020, Zhou et al., 2020, Zhou et al., 2020). A recent meta-analysis that included 1167 COVID-19 patients showed that conjunctivitis may be a sign of COVID-19 infection associated to a more severe form of disease, suggesting the use of protective equipment for all persons potentially exposed to infected subjects (Loffredo et al., 2020). Specifically, several studies reported conjunctival injection, chemosis and epiphora as the most common signs of ocular involvement in patients affected by COVID-19. In addition, the clinical picture could lead to a broad spectrum of symptoms, in particular foreign body sensation, dry eye and blurred vision (Xia et al., 2020; Wu et al., 2020, Chen et al., 2020b). In addition, it cannot be excluded that SARS-CoV-2 could infect both the eye and the surrounding structures; the role of the ocular surface as a potential access or exit route is under debate (Napoli et al., 2020, Aiello et al., 2020, Sun et al., 2020).

Ocular symptoms were common in a large series of COVID patients (Hong et al., 2020). Hong and collaborators investigated ocular symptoms through the Ocular Surface Disease Index and Salisbury Eye Evaluation Questionnaire in 56 patients, and found that fifteen (27%) had aggravated ocular symptoms, of which 6 (11%) had prodromal ocular symptoms before disease onset (Hong et al., 2020). The authors speculated that the micro-environment of the ocular surface and the stability of tear film could be affected by various factors, such as a

systemic immune system reaction to the SARS-CoV-2 infection, a secondary infection by opportunistic ocular pathogens, and infection of ocular tissues by the SARS-CoV-2 virus.

However, other studies have shown a lower prevalence of ocular surface involvement. In a large series of 535 COVID-19 patients, Chen and collaborators found that 27 patients (5.0%) presented with conjunctival congestion. The study also showed that dry eye, blurred vision and foreign body sensation were the most common ocular symptoms in all patients (20.9%, 12.7% and 11.8%, respectively) (Chen et al., 2020a). In another large sample of 1099 patients with COVID-19, 0.9% showed signs of ocular inflammation (Guan et al., 2020). Finally, Mungmungpantipantip et al., in a brief letter to the editor, reported that none of the 48 patients affected by COVID-19 presented any signs of ocular inflammation (Mungmungpantipantip & Wiwanitkit, 2020).

The presence of SARS-CoV-2 RNA at the level of the ocular surface has been investigated by means of RT-PCR on conjunctival swab samples. In particular, Seah and collaborators prospectively evaluated 17 patients with COVID-19, investigating tear samples and ocular findings during 2 weeks of active infection (Seah et al., 2020). All samples showed negative results for SARS-CoV-2 on viral isolation and RT-PCR, but 1 patient developed signs of ocular inflammation during hospitalization (Seah et al., 2020). Moreover, Zhou et al. tested 121 COVID-19 patients, disclosing three (0.8%) positive RT-PCR from conjunctival swabs (Zhou et al., 2020). Specifically, one patient showed both symptoms and positive conjunctival swab results and was classified as a critical case, and 2 patients showed no symptoms but revealed positive swab results, with one classified as a severe or critical case and another classified as moderate case (Zhou et al., 2020). Zhang et al. reported that only two out of 72 (2.8%) COVID-19 patients presented with conjunctivitis and that only one (1.4%) of them showed SARS-CoV-2 RNA fragments found in ocular discharges. The authors proposed that the incidence of SARS-CoV-2 infection through the ocular surface should be extremely low, whereas nosocomial infection of SARS-CoV-2 through the eyes after occupational exposure is a potential route (Zhang et al., 2020). Liang and coauthors evaluated 37 conjunctival swabs from confirmed SARS-CoV-2-infected patients. Three out of 37 patients (8.1%) had conjunctivitis. However, only one patient in serious condition, not suffering from conjunctivitis, presented a positive RT-PCR assay (Liang & Wu, 2020). Based on this finding, the authors suggested that conjunctival viral load could be directly proportional to severity of the disease (Liang & Wu, 2020).

Xia and coauthors prospectively evaluated the presence of SARS-CoV-2 in 30 affected patients (Xia et al., 2020) and disclosed a positive RT-PCR assay in two consecutive swabs from the only patient with conjunctivitis symptoms (Xia et al., 2020). On the contrary, Güemes-Villahoz showed that COVID-19 patients with and without conjunctivitis showed the same rate of positive samples from ocular fluids (5.5%), suggesting that the detection of SARSCoV-2 is not conditioned by the presence of conjunctivitis (Güemes-Villahoz et al., 2020a) (Güemes-Villahoz et al., 2020b). Wu et al. investigated ocular involvement and viral prevalence in the conjunctiva of 38 patients with COVID-19, and found that 12 patients (31.58%) presented with signs suggestive of conjunctivitis and that 5.26% of conjunctival specimens yielded positive findings for SARS-CoV-2 at RT-PCR. It should be considered that patients with positive conjunctival swabs presented ocular symptoms (Wu et al., 2020). Karimi and coauthors disclosed only one patient with conjunctivitis among 43 affected by COVID-19. However, three patients (7%), including the one with conjunctivitis, had tear samples positive for SARS-CoV-2 (Karimi et al., 2020). These results suggest that, although ocular manifestation seems to be rare in COVID-19 patients, the possibility of ocular transmission should be considered even in the absence of ocular manifestations. Fang et al. found that five (15.63%) out of 32 patients with COVID-19 showed positive SARS-CoV-2 RNA via RT-PCR tear swabs. However, they did not investigate the potential ocular involvement of affected patients (Fang et al., 2020). Xie et al. performed ocular surface swabs on 33 consecutive COVID-19 patients without any ocular manifestation and found that SARS-CoV-2 tested highly positive in both eyes from 2 patients (Xie et al., 2020). These findings demonstrated that SARS-CoV-2 RNA could be detected from the normal ocular surface of COVID-19 patients.

Table 1 summarizes the characteristics and main findings of studies (published as of June 2, 2020) that evaluated ocular surface involvement in patients with COVID-19 infection. In the thirteen studies taken into consideration, only 70 patients (3.2%) out of 2176 COVID-19 patients were diagnosed as suffering from ocular surface involvement.

It should be considered that most of these studies suffer from a retrospective design. In addition, because this is a potentially lethal disease and because hospitalization often requires careful systemic monitoring, the presence of signs of ocular inflammation may have been clinically underestimated. Furthermore, sampling time during the course of infection was found highly variable across studies, whenever indicated. The diagnostic window for molecular-based techniques (and serological testing) has been clarified only recently (Younes et al., 2020), and it is also highly feasible that this fundamental parameter may have been missed in the

ophthalmological studies performed in the early, very troubling period of the SARS-CoV-2 pandemic. In addition, and closely related to the ocular surface site, late sampling may have activated the immune system with significant increases in tears containing immunoglobulins exuded from plasma and antimicrobial compounds which can inhibit viral binding to ACE2 (Lang et al., 2011, Orr-Burks et al., 2014).

These observations suggest that the ocular surface as a potential portal of entry for this virus should not be underestimated, as the possibility that the conjunctiva might be a gate for the virus is consistent with biological findings so far. In addition, the possibility of disease transmission through the ocular surface should be considered even in the absence of ocular manifestations.

OCULAR SURFACE AND LABORATORY DIAGNOSIS OF COVID-19: CURRENT ISSUES AND CHALLENGES

Inefficient diagnostic methods have been accused of being responsible for the variability of coronavirus findings on the ocular surface (Zhang et al., 2020). A detailed discussion of the several technical issues that could be involved is beyond the scope of this paper. An exhaustive discussion of this issue has been conducted by previous studies (Deeks et al., 2020, Sethuraman, Jeremiah & Ryo, 2020, Tang et al., 2020). In addition, data on technical aspects are almost totally lacking in the papers published to date dealing with tear or conjunctival samples in SARS-CoV2 detection.

We would like here to briefly mention some arguments that deserve further study:

- Viral load in tears. Current RT-PCR protocols may have low sensitivity in detecting SARS-CoV-2 in conjunctival and tear samples. This could be related to small amounts of viral RNA in these secretions, taking into account that it reflects a disease course-dependent balance between viral replication and immune system response, as was previously shown for MERS-CoV (Memish et al., 2014). Furthermore, MERS-CoV concentration and genome fraction was shown to be dissimilar in different sites of the respiratory tract (Memish et al., 2014). When distribution of SARS-CoV-2 was investigated in bronchoalveolar fluid, pharyngeal swabs, blood, sputum, feces, nasal samples, and urine of patients clinically diagnosed as COVID-19 positive, virus was detected all tissues except urine, with the highest viral load in nasal swabs [mean cycle threshold value of 24.3 (1.4×10^6 copies/mL) as compared to more than 30 ($<2.6 \times 10^4$ copies/mL) in all the other tissues] (Wang et al., 2020). Interestingly, a recent meta-

analysis showed that the sensitivity of saliva samples is slightly lower than that of nasopharyngeal samples (91% compared to 98%), suggesting that it may be an effective method for the detection of SARS-CoV-2, with less heterogeneity among studies (Czumbel et al., 2020). On the whole, data on the accuracy of RT-PCR testing suggest that test sensitivity may vary by type of specimen, but these data did not include tears.

- Sampling time. Some authors reported that conjunctival samples collected in the late phase of the disease are CoV RNA-negative (Chan et al., 2004). The contribution of antimicrobial agents increasing post-infection, as reported above, may contribute to support CoV RNA as present only in the early phase of the disease. MERS-CoV RNA in the conjunctiva had been detected within only 6 days post-infection in an animal model (de Wit et al., 2016). A high percentage of positivity was found in tears or conjunctiva sampled from the 4th to 9th day (median value being 5th) from the onset of symptoms (Arora et al., 2020), with a significant decrease in positivity from the second week and beyond (Seah et al., 2020, Zhang et al., 2020). Other authors have noted that the positivity of eye swabs to SARS-CoV-2 was prolonged over time (Colavita et al., 2020), remaining for over two weeks after nose and pharyngeal swabs had become negative (Hu et al., 2020).

Taken as a whole, studies with a large sample size and repeated collection of conjunctival/tears in each patient during the course of the disease are needed.

Collection technique may be appropriate or standardized: most of the studies have reported conjunctival swabs for tear collection (Arora et al., 2020, Karimi et al., 2020, Wu et al., 2020, Xia et al., 2020, Zhou et al., 2020), except one where the Schirmer test was used (Seah et al., 2020). For specimen sampling, the World Health Organization recommends (CDC 2020) the use of only synthetic fiber swabs rather than calcium alginate swabs which may contain substances interfering with PCR testing. Similarly, topical anesthesia is not recommended for tear and conjunctival sample collection, as it might negatively influence viral viability (CDC 2020).

Primer design: hundreds of TaqMan RT-PCR assays for the detection of SARS-CoV-2 have been proposed and dozens are under development for both manual and automated assay (<https://www.finddx.org/covid-19/pipeline>). Furthermore, scientific validation of their diagnostic accuracy, tailored to the specimen sampled, including tears and conjunctiva, should be performed in real-life prospective trials.

In summary, there is strong evidence that SARS-CoV-2 can affect the ocular surface. Because of its anatomical and functional structure, the ocular surface could represent a potential infection route and allow both the entry and exit of the virus. To date, studies on the involvement of the ocular surface have given conflicting results, and there is still no consensus on the methodological techniques to be applied to effectively detect SARS-CoV-2 at the ocular level. Testing of specimens from multiple sites, including the ocular surface, and the standardization and validation of a method for the detection of SARS-CoV-2 may improve sensitivity and reduce false-negative test results, with the aim of implementing management of the disease at all stages (Ho et al., 2020).

Ahead of print

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Ahead of print

Table 1. Characteristics and main findings of studies evaluating ocular surface involvement in patients with COVID-19 infection.

Author	Design	Patients (n)	Ocular Involvement (no. patients) %	Positive Ocular Surface Swabs	Ocular Swabs Timing
Chen et al., 2020a	Retrospective	535	(27) 5%	NP	
Fang et al., 2020	Retrospective	32	NP	15.6%	NA
Guan et al., 2020	Retrospective	1099	(10) 0.9%	NP	
Güemes-Villahoz et al., 2020	Cross-sectional	36 (18 with ocular involvement + 18 without ocular involvement)	NA	5.5% in each group	NA
Hong et al., 2020	Retrospective	56	(15) 27%	NP	
Karimi et al., 2020	Prospective	43	(1) 2.3%	7 %	1–7 days
Liang & Wu, 2020	Retrospective	37	(3) 8.1%	1%	NA
Mungmungpantip&Wiwani tkit 2020	Retrospective	48	0%	NP	
Seah et al., 2020	Prospective	17	(1) 5.8%	0%	3-20 days
Wu et al., 2020	Retrospective	38	(12) 31.5%	5.2%	NA
Xia et al., 2020	Prospective	30	(1) 3.3%	3.3%	3-16 day
Xie et al., 2020	Retrospective	33	0%	6.1%	1-7 days
Zhang et al., 2020	Cross Sectional	72	(2) 2.8%	1.4%	6-46 days
Zhou et al., 2020	Retrospective	121	(7) 6.6%	0.8%	1-38

NP: Not performed, NA: Not applicable

Figure 1. Ocular tropism of respiratory viruses and SARS-COV and SARS-COV-2 receptors. Ocular tissues exhibiting tropism for respiratory viruses are shown along with the location of the receptors that mediate the entry of SARS-COV and SARS-COV-2.

