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SARS-CoV-2 on the ocular surface: is it truly a novel transmission route?

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ABSTRACT

Since December 2019, the novel COVID-19 outbreak has spread rapidly around the globe and infected millions of people. Although the major transmission route of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered to be airborne droplets and close contact, the ocular transmission route has been reported with great concern. The current work summarises the characteristics of SARS-CoV-2, the ocular distribution of the major SARS-CoV-2 binding protein, and the experimental and clinical evidence of the ocular transmission route. Although it seems that the likelihood of the ocular surface being an infection gateway is low, SARS-CoV-2 infection or transmission via the ocular surface may cause conjunctivitis and other ocular discomfort. Therefore, good eye protection is an essential safeguard procedure, especially for medical staff.

INTRODUCTION

In early December 2019, a novel coronavirus (CoV), referred to as 2019-nCoV, became the infection source of the recent pandemic COVID-19. As of 29 May 2020, the total number of confirmed cases worldwide reached 5 920 608, with 2 574 220 cured cases and 362 431 deaths. This virus is a novel beta-coronavirus (BCoV) that resembles severe acute respiratory syndrome coronavirus (SARS-CoV).¹ Therefore, the Coronavirus Study Group updated the virus to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).² Despite its rapid spread worldwide, the clinical characteristics of the SARS-CoV-2 infection disease remain largely unclear. Generally, SARS-CoV-2-infected patients develop respiratory disorders and experience initial symptoms of fever, coughing and fatigue, which quickly progress to pneumonia.³ However, extra-pulmonary manifestations were observed in several patients at the onset of the illness, such as headache, diarrhoea, nausea and vomiting,⁴ and some patients presented with an asymptomatic infection.⁵ These issues pose great challenges to disease diagnosis and pandemic control, and necessitate a better understanding of SARS-CoV-2.

Similar to the transmission of SARS-CoV, the main spreading path of SARS-CoV-2 seems to be in close contact with an infected person and via airborne droplets or contact with fomite.⁶ The potential transmission routes include aerosol and gastrointestinal transmission.⁷ On 6 February 2020, Lu *et al*⁸ commented that the transmission of SARS-CoV-2 through the eyes must not be overlooked. Thereafter, numerous

studies were performed to find evidence of this potential transmission route. There is a need for heightened investigations of SARS-CoV-2 binding protein expression on the ocular surface and a greater understanding of how ocular exposure routes influence disease presentation and progression in human beings.

WHAT IS SARS-COV-2?

The phylogenetic analysis showed that SARS-CoV-2 belongs to the bBCoV genera, which primarily infects mammals. The spike proteins (S) are critical for the binding to host cell receptors and facilitate entry into host cells. In comparison with the full genomic sequences of SARS-CoV-2, BCoV sequences show 96.2% similarity, which suggests that bats may be the zoonotic origin of SARS-CoV-2.^{9 10} High-throughput sequencing and a real-time reverse-transcription PCR (RT-PCR) assay revealed that SARS-CoV-2 was closely related (88%) to two bat-derived SARS-like CoVs, bat-SL-CoVZC45 and bat-SL-CoVZXC21, which were collected in 2018 in Zhoushan, eastern China. However, SARS-CoV-2 was far from SARS-CoV (approximately 79%) and Middle East respiratory syndrome coronavirus (MERS-CoV, approximately 50%).¹ Therefore, current evidence suggests that bats were likely the native hosts of SARS-CoV-2. Ji and colleagues¹¹ suggested that snakes were another likely host for SARS-CoV-2, but this hypothesis was widely questioned. Further research is needed to determine the animal that was the intermediate host in the transmission cascade from bats to humans.

MOLECULAR DIAGNOSIS OF SARS-COV-2

An analysis of clinical samples from patients with new viral infections is critical for confirmation of their diagnosis. According to Koch's traditional hypothesis, virus isolation is the gold standard for the laboratory diagnosis of viruses. We summarised the different studies performed on the CoV based on CoV type, detection method, sample type and detection time (day after onset), and analysed whether the CoV infection was associated with conjunctivitis (table 1). We found that RT-PCR was the main laboratory method used for the diagnosing of CoV infection. Other methods, including ELISA and gene sequencing, are also very reliable.^{8 12-14}

RT-PCR testing of conjunctival swabs was the most commonly used approach to determine the ocular characteristics of SARS-CoV-2-infected patients. However, the positive rate of the molecular diagnosis of tear viruses may be low. Ziad and

Table 1 Detection methods for coronaviruses

Coronavirus	Method	Sample	Timing (days after onset)	References	Conjunctivitis	
SARS-CoV	ELISA	Tear (conjunctival swabs)	7–10 days	13	Not reported, but RT-PCR and ELISA detection of patient's tears were positive.	
		Blood serum				
	PCR	Tear (conjunctival swabs)	12 days	21		
		RT-PCR	Blood serum	In the second week		22
			Respiratory secretions			
			Urine			
		Stool				
		Lung tissue				
SARS-CoV-2	RT-PCR	BALF			Reported, RT-PCR conjunctival swab results were positive in a small range of patients.	
		Deep sputum		17		
		Conjunctival swabs		23		
	RT-PCR	Upper respiratory secretions (nasopharyngeal and oropharyngeal swabs)	4 days	24		
		Serum	11 days			
		Stool	7 days			
		ELISA	Blood serum	Acute phase, remission phase	13	
	Gene sequencing	Blood serum		12		
	HCoV-NL63	RT-PCR	Respiratory samples (nasal aspirates and swabs)		25	Reported; no detection of eye tissue was reported
		Gene sequencing	Nasopharyngeal aspirate specimen	5 days	14	
MERS-CoV	RT-PCR	Respiratory tract samples, such as nasopharyngeal swab, sputum, deep tracheal aspirate, etc		26	Not reported	

BALF, bronchoalveolar lavage fluid; HCoV-NL63, human coronavirus NL63; MERS-CoV, Middle East respiratory syndrome coronavirus; RT-PCR, reverse-transcription PCR; SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

colleagues¹⁵ found that tracheal aspirates yielded significantly higher virus loads compared to nasopharyngeal swab and sputum specimens, which means that viral concentrations and genome fractions vary in different sites of the body. Tear samples came from the plasma, and their total concentration was small. The concentration of the virus in tears may be significantly lower than the respiratory samples. Chen and colleagues¹⁶ found that the viral RNA levels in conjunctival specimens were dramatically lower than the respiratory samples. Even pharyngeal swab PCR had a single positive rate of only approximately 30%, and the positive rate for tears may be much lower. Therefore, it is challenging to detect SARS-CoV-2 on the ocular surface due to its lower viral load and limited sample volume.

To improve the sensitivity of molecular diagnosis methods, several other techniques are under development. Monoclonal antibodies, which use specific antibodies to recognise virus antigens in tears and blood, may be another sensitive detection method for the identification of SARS-CoV-2-related antigens.^{13–17} RT-loop-mediated isothermal amplification can also rapidly diagnose CoV.¹⁸ Broughton *et al*¹⁹ recently uploaded a protocol for the detection of COVID-19 using CRISPR diagnostics online. However, this technique is not ready for clinical use. Therefore, collecting tears or conjunctival swabs for a series of molecular tests provides a more objective and accurate examination of whether the new virus will infect the eyes. Droplet digital PCR may help evaluate disease progression via the quantitative monitoring of viral load in lower respiratory tract samples.²⁰

HOW DOES SARS-COV-2 MAKE INDIVIDUALS INFECTIOUS?

Notably, structural analyses suggest that SARS-CoV-2 enters host cells via ACE2 as the potential host receptor.²⁷

Co-immunoprecipitation and ELISA also confirmed the binding of CD147 and SARS-CoV-2 spike protein.²⁸ Therefore, cells expressing ACE2 or CD147 may be the potential targets for infection. Although ACE2 mRNA exists in almost all organs, its protein expression is largely unknown. Based on the rich knowledge of SARS-CoV and the new sequence of SARS-CoV-2, scientists analysed the potential receptor of SARS-CoV-2.²⁹ Previous studies reported that SARS-S used ACE2 as an entry receptor and the cellular serine protease TMPRSS2 for S-protein priming.^{30–31} Despite replacing four of the five important interface amino acid residues, the SARS-CoV-2 S-protein had significant binding affinity for human ACE2.^{27–32} Wan *et al*²⁹ also reported that several critical residues in the SARS-CoV-2 receptor-binding motif (RBM) (particularly Gln493) provided favourable interactions with human ACE2, which is consistent with the capacity of SARS-CoV-2 for human cell infection. Several other residues in SARS-CoV-2 RBM (particularly Asn501) are compatible with, but not ideal for, binding human ACE2, which suggests that SARS-CoV-2 acquired some capacity for human-to-human transmission.²⁹ Therefore, ACE2 and TMPRSS2 currently represent the major players for cell entry.^{33–34} Ziegler *et al*³⁵ recently identified ACE2 and TMPRSS2 co-expressing cells in lung type II pneumocytes, ideal absorptive enterocytes and nasal goblet secretory cells. Their experiment data of viral infection in vitro and in vivo showed that SARS-CoV-2 exploited the species-specific interferon-driven upregulation of ACE2, which is a tissue-protective mediator during lung injury, to enhance infection. Sungnak *et al* similarly revealed that SARS-CoV-2 entry factors were highly expressed in nasal epithelial cells together with innate immune genes.³⁶ Zhou *et al*³⁷ also confirmed the expression of ACE2 and TMPRSS2 on ocular surface cells, including conjunctiva and cornea.

IS ACE2 PRESENT IN THE EYES?

To determine the potential route of SARS-CoV-2 infection on the ocular surface, we summarised and analysed the distribution of ACE2 in eyes (table 2). SARS-CoV-2 has a stronger contagious characteristic than SARS-CoV, and its mechanism of human-to-human spread may be related to ACE2.³⁸ Sun *et al*³⁹ found ACE2 expression in human cornea and conjunctival tissues, but its levels were lower than in heart and lung tissues. They also found that ACE2 expression in conjunctiva and corneal cells was primarily located in the cytoplasm and less expressed on the cell membrane.⁴⁰ Several studies showed that an activator of ACE2, diminazene aceturate, was recently patented for the treatment of glaucoma and uveitis. However, the main sites of action may be the ciliary bodies, uvea, photoreceptor layer, outer and inner plexiform layers, ganglion cell layer and retinal pigment epithelial cells.^{41–42} All of these results are evidence of ACE2 expression on the eye.

Zhou *et al*³⁷ analysed protein levels of ACE2 and TMPRSS2 in human postmortem eyes and surgical specimens. Across all eye specimens, immunohistochemical analysis revealed the expression of ACE2 in the conjunctiva, limbus and cornea, with especially prominent staining in the superficial conjunctival and corneal epithelial surface. Surgical conjunctival specimens also showed ACE2 expression in the conjunctival epithelium, which was especially prominent in the superficial epithelium and the substantia propria. All eye and conjunctival specimens also expressed TMPRSS2.³⁷ Western blot analysis of protein lysates from human corneal epithelium obtained during refractive surgery confirmed the expression of ACE2 and TMPRSS2. Their results revealed that ocular surface cells, including conjunctiva, were susceptible to SARS-CoV-2 infection, and these cells may serve as a portal for entry and reservoir for person-to-person transmission of this virus.

IS CD147 DISTRIBUTED IN THE EYES?

CD147, also known as Basigin or extracellular matrix metalloproteinase inducer, is a transmembrane glycoprotein that is associated with viral infection. Previous studies showed that CD147 played a functional role in promoting SARS-CoV invasion into host cells. Chen and colleagues²⁸ found that CD147 was a new SP receptor, and the interaction between CD147 and SP facilitates SARS-CoV-2 invasion of host cells. ACE2 and CD147 were also expressed on the ocular surface. Immunohistochemical studies showed that CD147 was detected in the epithelium and endothelium of the cornea, conjunctiva, corneal stromal cells and retinal pigment epithelial cells.⁴⁷ CD147 is also expressed in human corneal epithelial cells and pigment epithelial cells, and it is present in tears, aqueous humour and vitreous fluids.⁴⁷ CD147 plays a crucial role in the formation and maintenance of tissue epithelial structure in dry eye disease, and it may be essential for the formation and maintenance of an organised epithelial structure.⁴⁸ CD147 is primarily expressed in the basal cells in the meibomian gland of the human eye, and it plays an important

role in the differentiation and structural integrity of the meibomian gland. CD147 also plays an important role in the regulation of meibomian gland function.⁴⁹ A unique distribution of lactate transporters is found in the retinal pigment epithelium, and these transporters regulate lactate levels of the outer retina.⁵⁰ These results provide a molecular basis for the propagation of SARS-CoV-2 through the ocular surface. Table 3 displays the distribution of CD147 in human eyes.

IS SARS-COV-2 TRANSMITTED AND INFECTED THROUGH THE OCULAR SURFACE?

Respiratory viruses cause a broad spectrum of diseases in humans, including several ocular tropisms. The main reason is that infectious droplets and body fluids easily contaminate the human conjunctival epithelium.⁵¹ Notably, hand–eye contact may increase the risk of contracting the virus from the hand. Therefore, we analysed the probability of an ocular transmission route.

Link between the ocular and respiratory systems

Several anatomical properties indicate the eye as a potential site of virus infection and a gateway for respiratory infection. The nasolacrimal system provides a significant anatomical bridge between the ocular and respiratory systems.⁵² Based on this bridge, tear fluid from the ocular surface is transported to the inferior meatus of the nose, which facilitates viral movement from the ocular surface to the respiratory tract. The ocular mucosal immune system and nasolacrimal ducts further share immunological interdependence.⁵³ As previously reviewed,⁵⁴ beyond the anatomical relationship between the ocular and respiratory systems, the structure and distribution of the cellular receptors in these systems likely contribute to the tissue tropism of respiratory viruses, such as when host epithelial cell

Table 3 Distribution of extracellular matrix metalloproteinase inducer (EMMPRIN; CD147) in human eyes

Position	References
Anterior eye	
Tear	47
Aqueous humour	47
Cornea	47
Conjunctiva	47, 48
Meibomian gland	49
Posterior eye	
Retina	47
RPE	50
Nerve fibres in optic nerve head	47
Vitreous body	47

RPE, retinal pigment epithelium.

Table 2 Distribution of ACE2 in eyes

	Anterior eye				Posterior eye					References	
	Aqueous humour	Cornea	Conjunctiva	Ciliary body	Vitreous body	Retina	Retinal pigment epithelium cells	Photoreceptor layer	Outer and inner plexiform layers		Ganglion cell layer
Human	+	+	+			+					39–43, 45
Rat				+		+	+	+	+	+	42, 46
Rabbit		+	+								39, 44
Porcine				+	+	+					41

glycoproteins bearing terminal sialic acids are distributed throughout the human respiratory tract and ocular tissue. These factors indicate that other ocular discharges containing the virus may drain to the respiratory tract through the lacrimal passage and cause the patient to become infected with pneumonia. Qing *et al*⁵⁵ discussed that the virus entered the tears through droplets that may pass through the nasolacrimal ducts and into the respiratory tract. Despite intensive work focused on understanding the relationship between the ocular and respiratory systems, further research is needed to better understand the relationship between ocular and respiratory manifestations of SARS-CoV-2 infection.

Virus infection on the ocular surface

Ocular diseases associated with herpesvirus type 1 and feline calicivirus are not unusual in animals. Conjunctivitis, or 'pink eye', is the most commonly reported clinical symptom after virus infection on the ocular surface. Jean *et al*⁵⁶ found that conjunctivitis was the most common ocular condition, followed by corneal epithelial ulceration and keratitis with or without ulceration. However, ocular manifestations of feline CoV consist predominantly of uveitis and chorioretinitis with associated fibrinous exudate in the anterior ocular chamber.⁵⁷ In humans, avian and human influenza A viruses show a capacity to use the eyes as a portal of entry and spread ocular disease. Like the respiratory tract, the ocular surface (notably the corneal and conjunctival epithelia) represents a mucosal surface that provides a pathway for viral entry.⁵⁸ Other viruses that cause conjunctivitis in humans are also very common, such as the mumps virus,⁵⁹ respiratory syncytial viruses⁶⁰ and subtype H7 viruses.⁶¹ During the SARS outbreak, researchers also found that RT-PCR and ELISA detection of patient's tears were positive.^{13 59} Therefore, the ocular surface is actually quite vulnerable to respiratory viruses. In the SARS-CoV-2 epidemic area, SARS-CoV-2-related eye infections must be seriously and carefully evaluated.

Animal model research of SARS-CoV, MERS-CoV and SARS-CoV-2 in the conjunctiva

The study of mammalian models that recapitulate human disease has greatly improved our understanding of the pathological processes involved in infection and disease through ocular routes. Therefore, animal models were used to investigate the mechanism of SARS-CoV infection. *Cynomolgus* macaques were infected with SARS-CoV through the nostril and bronchus, the inferior conjunctival fornix of each eye or the saphenous vein, and their chest radiographs peaked between 8 and 10 days postinfection (dpi). Among the three groups, James and colleagues⁶² found that

conjunctival-infected animals had more positive specimens than intravenous inoculation. However, there were some potential limitations to this study. First, there was only a small number of animals included in each group, and the entire spectrum of disease severity was not observed. Second, a relatively high inoculum of virus was used in the study. Nonetheless, these limitations did not affect our conclusions that the conjunctiva may be a route of transmission, although this route is less likely.

In a rhesus macaque model, the widespread dissemination of MERS-CoV occurred through the respiratory tract. MERS-CoV RNA was detected in the conjunctiva, but viral loads were no longer be detected in the conjunctiva 6 dpi.⁶³ This result suggests that the conjunctival scraping test should be performed as early as possible if ocular symptoms in a patient with COVID-19 or suspected case are identified.

Deng and colleagues⁶⁴ recently found that macaques can be infected with SARS-CoV-2 via the conjunctival route. The viral load and distribution in the conjunctival infected-macaque were comparatively high in the nasolacrimal system but relatively mild and local in the lung compared to macaques that were inoculated via intratracheal routes, which provides strong evidence that conjunctivitis was the possible route for SARS-CoV-2 infection.

Clinical data of SARS-CoV-2 infected on the ocular surface

There have been a small number of reports of SARS-CoV-2-infected conjunctivitis. Table 4 summarises these studies by the number of patients (confirmed/suspect), number of patients with viral conjunctivitis, SARS-CoV-2 RNA tested in tears and/or conjunctival secretions, and conjunctival swabs sampling time (after the onset of SARS-CoV-2 infection).

The epidemiological data on the incidence of conjunctivitis in patients with COVID-19 range from 0.8% to 4.8%.⁶⁵⁻⁶⁷ Few cases reported conjunctivitis as the initial medical presentation in patients with COVID-19.⁶⁷ The ocular manifestations of SARS-CoV-2-related conjunctivitis include conjunctival hyperaemia, ocular irritation, foreign body sensation, epiphora and chemosis. Wu *et al*⁶⁸ found that these symptoms more commonly affected patients with severe systemic symptoms of COVID-19. Notably, the secretion of virus in tears always occurred during the early phase of the disease, which is similar to patients with SARS.²¹

Although positive SARS-CoV-2 RNA testing results in tears and/or conjunctival secretions are more likely to be found in patients with viral conjunctivitis, Xie *et al*⁶⁹ also reported two cases with strong positive SARS-CoV-2 testing results without conjunctivitis. Similarly, Zhou *et al*²³ reported two probable positive cases with no symptoms of conjunctivitis. Therefore,

Table 4 Clinical data of SARS-CoV-2 infected on the ocular surface

No.	Reference detail	Patients, n (confirmed/suspect)	Patients with viral conjunctivitis (n)	SARS-CoV-2 RNA tested in tears and/or conjunctival secretions	Conjunctival swabs sampling time (after the onset of SARS-CoV-2 infection)
1	Zhou <i>et al</i> ²³	67 (64/3)	1	2 Cases probable positive (negative for the patients with conjunctivitis)	NA
2	Zhang <i>et al</i> ⁶⁷	102 (72/30)	2	1 Case positive	Day 3 for CoV positive
3	Xia <i>et al</i> ⁶⁶	30 (30/0)	1	1 Case positive	Days 2 and 5 (sampled twice for the same patient)
4	Wu <i>et al</i> ⁶⁸	38 (38/0)	12	2 Cases positive	NA
5	Chen <i>et al</i> ¹⁶	1 (1/0)	1	1 Case positive	Days 13, 14 and 17 for CoV positive, Day 19 for CoV negative
6	Cheema <i>et al</i> ⁷⁰	1 (1/0)	1	1 Case weakly positive	Sampled on Day 5, tested on Day 7
7	Xie <i>et al</i> ⁶⁹	33 (33/0)	0	2 Cases strong positive	1 Case on Day 4, 1 case on Day 5
8	Li <i>et al</i> ⁷³	2 (2/0)	2	1 Case positive	1 Case (positive) on Day 1, 1 case on Day 4

SARS-CoV2, severe acute respiratory syndrome coronavirus 2.

SARS-CoV-2 may exist in conjunctival eyes and on the normal ocular surface of patients with COVID-19, which suggests that SARS-CoV-2 is spread through conjunctival contact.

There are several cases where patients had conjunctivitis symptom, but the SARS-CoV-2 RNA testing of tears and/or conjunctival secretions were negative. The reason behind these results may be associated with the sampling time, the collection of few exfoliated cells and the lack of sensitivity of the RT-PCR kits.

Apart from conjunctivitis, patients may also develop other ocular discomfort or disease. Cheema *et al*⁷⁰ reported a case where keratoconjunctivitis was the initial medical presentation. Hong *et al*⁷¹ recruited 56 confirmed patients to investigate detailed ocular symptoms, including eye itching, sore eye, dry eye and floaters. In their study, 15 (27%) patients had aggravated ocular symptoms and 6 (11%) patients had prodromal ocular symptoms before disease onset. Chen *et al*⁷² recently performed a cross-sectional study of 534 cases with COVID-19 in Wuhan. Of the total 534 patients with COVID-19, conjunctival congestion (4.68%), dry eye (112, 20.97%), blurred vision (68, 12.73%) and foreign body sensation (63, 11.80%) ranked as the top four.

The recent results show that SARS-CoV-2 is capable of causing ocular complications. Ocular symptoms may appear just before the onset of respiratory symptoms. SARS-CoV-2 RNA testing is best performed in the early days after onset. Although no researches compared the disease outcomes of patients who were infected through ocular transmission route and respiratory transmission route, all of these clinical data showed that after topical antiviral treatment, pink eyes or conjunctivitis quickly return to normal. Therefore, we suspected that the patients infected through ocular transmission route might recover more quickly, and the disease outcomes are better than infected through respiratory transmission route.

HOW DO YOU PROTECT AGAINST SARS-COV-2 INFECTION VIA THE OCULAR SURFACE?

Wang *et al*⁷⁴ recently reported that 138 hospitalised SARS-CoV-2-infected pneumonia cases had a hospital-associated transmission rate of 41%, among whom 70% were healthcare professionals. The main risk factor for the nosocomial infection of medical staff members who provided nursing care to the intubated patients with SARS was whether they wore protective goggles (1% of the clinicians wearing eye protection were infected versus 8% of the clinicians who did not).⁷⁵ Considering the common feature of sporadic cases and the higher viral aerosol load in the hospital, the ocular transmission route in hospitals should be seriously considered. A lack of eye protection may lead to ocular surface exposure or facial skin exposure, which may then spread from the facial skin to the hands and other mucous membranes. Therefore, in addition to regular masks, gowns and gloves, goggles and frequent handwashing are essential protective measures, especially for medical staff in close contact with patients with COVID-19.

CONCLUSION

In conclusion, the main question in the present review was whether SARS-CoV-2 can infect or be transmitted through the ocular surface. We summarised the structure, molecular diagnostic methods and infection mechanisms of SARS-CoV-2, and presented a summary of the distribution of ACE2 and CD147 in eyes. Based on the anatomical features of the ocular and respiratory systems and the experimental and clinical evidence of

CoV-related ocular disease, we conclude that the likelihood of the ocular surface being an infection gateway is low, but SARS-CoV-2 infection or transmission through the ocular surface may be a potential infection route, especially in hospitals. Therefore, good eye protection is an essential safeguard procedure, especially for medical staff. Only through this measure can healthcare professionals be better protected against non-combatant attrition.

Correction notice This paper has been amended since it was published. The following credit has been added: XC and HY contributed equally to this manuscript.

Contributors XC and HY participated in the research design, data acquisition/research execution, data analysis/interpretation and manuscript preparation. TM, BC, LC and SL participated in the data acquisition and manuscript revision. XZ and XS supervised the manuscript.

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