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Role of the eye in transmitting human coronavirus: what we know and what we do not know

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ABSTRACT

The outbreak of recently identified 2019 novel coronavirus (2019-nCOV) infection has become a world-wide health threat. Currently, more information is needed for further understanding the transmission, clinical characteristics, and infection control procedures of 2019-nCOV. Recently, the role of the eye in transmitting 2019-nCOV has been intensively discussed. Previous investigations about other high infectious human COVs, that is, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), may provide helpful information. In this review, we describe the genomics and morphology of human CoVs, the epidemiology, systemic and ophthalmic manifestations, mechanisms of human CoVs infection, and infection control procedures. The role of the eye in the transmission of SARS-CoV and 2019-nCOV is discussed. Although the conjunctiva is directly exposed to extraocular pathogens, and the mucosa of ocular surface and upper respiratory tract is connected by nasolacrimal duct and share same entry receptors for some respiratory viruses. The eye is rarely involved in human CoVs infection, conjunctivitis is quite rare in patients with SARS-CoV and 2019-nCoV infection, and COV RNA positive rate by RT-PCR test in tears and conjunctival secretions from patients with SARS-CoV and 2019-nCoV infection is also very low, which imply that the eye is neither a preferred organ of human COVs infection, nor is a preferred gateway of entry for human COVs to infect respiratory tract. However, pathogens exposed to the ocular surface might be transported to nasal and nasopharyngeal mucosa by constant tear rinsing through lacrimal duct, and then cause respiratory tract infection. Considering close doctor-patient contact is quite common in ophthalmic practice which are apt to transmit human COVs by droplets and fomites, hand hygiene and personal protection are still highly recommended for health care workers to avoid hospital-related viral transmission during ophthalmic practice.

KEY WORDS: Coronavirus; 2019-nCOV; transmission; infection; conjunctiva; eye

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INTRODUCTION

Coronavirus (CoV) is an enveloped single-stranded positive-sense RNA virus which typically causes respiratory and enteric infections affecting both human and wild animals[1-3]. Since first identified in 1960s, Human CoVs were considered relatively benign and usually cause mild upper respiratory tract infections (common cold) until the emergence of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and later the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012[4]. The latter two CoVs could result in severe lower respiratory tract infection which would rapidly progress to pneumonia and caused thousand of cases and hundreds of deaths in about 30 countries, respectively[2,4]. In December 2019, another outbreak of highly infectious pneumonia caused by a novel coronavirus (2019-nCOV, now named as SARS-CoV-2) emerged in Wuhan, China, and has soon become a major global health concern[2, 3].

Currently, more detailed information about the transmission of 2019-nCOV is urgently needed to prevent its pandemic spread. Human CoVs mostly spread through respiratory droplets expelled by the infected individuals and direct contact with virus-contaminated fomites[4]. The conjunctiva of the eye is easily exposed to infectious droplets and fomites during close contact with infected patients or contaminated hands. Hence, conjunctiva is postulated to be an important portal of entry for Human CoVs, while tear and ocular secretions may contain virus and spread viral infection[4, 5]. However, the role of the eye in the transmission of human CoVs is still under discussion, for considerable controversy exists. This review presents the genomics and morphology of human CoVs, the epidemiology, systemic and ophthalmic manifestations, and mechanisms of human CoVs infection, as well as the role of the eye in the transmission of human CoVs. Infection control procedures and personal protective equipments against human CoVs transmission in ophthalmic practice are also reviewed.

GENOMICS

CoVs have an enveloped single positive-strand RNA genome with a 5′-terminal cap structure and a poly(A) sequence at the 3′-end. CoV genome is approximately 30 kb (27~32 kb) long, and is the largest RNA genome known so far[1,4,6]. CoVs belong to the family *Coronaviridae* and the order *Nidovirales*, and are classified into four genera: Alphacoronavirus (α-CoV), Betacoronavirus(β-CoV), Gammacoronavirus

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(γ-CoV), and Deltacoronavirus (δ-CoV). CoVs mainly cause respiratory and enteric infections in wild animals, domestic animals, and humans. Animal CoVs from the genera α-CoV and β-CoV mainly infect mammals such as dogs, cats, pigs, and bats, while CoVs in the genera γ-CoV and δ-CoV primarily infect birds[1,6,7].

Until now, a total of 7 human CoVs have been identified, that is, HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1,SARS-CoV, MERS-CoV, and recentently identified 2019-nCOV[1-3, 6-8]. The former two human CoVs belong to the genus α-CoV, and the latter five human CoVs belong to the genus β-CoV. Three recently identified human CoVs, that is, SARS-CoV, MERS-CoV, and 2019-nCOV, have been recognized as highly infectious zoonotic viruses transmitting between animals and human. Recent studies revealed that SARS-CoV was transmitted from civet cats to humans, MERS-CoV from dromedary camel, and 2019-nCOV probably from pangolin[1,2,6-9]. Recent investigations implicated that the bats were most possibly the natural reservoir of SARS-CoV, MERS-CoV, and 2019-nCOV[1,6,9-11]. Genome sequence analysis revealed that the 2019-nCoV was distinct from SARS-CoV (about 79% identity) and MERS-CoV(about 50% identity), yet more closely related to SARS-like- CoVs (about 88% identity) in bats[10,11].

MORPHOLOGY

The CoV particles have a spherical or elliptical shape with a diameter of about100 nm (50~200nm). They carry three major structural proteins (S, M, and E) in the envelope and contain a helical nucleocapsid that is formed by the viral genomic RNA and the viral N protein. The viral spike protein has receptor-binding and fusogenic functions, and is essential for initiation of CoV infection[1,8,12-14]. Further three-dimensional structure analyses suggest that spike protein is composed of two subunits: S1, which mediates SARS-CoV binding to receptors on host cell membranes, and S2, which triggers the membrane fusion between the virus and host cells [11,13].

EPIDEMIOLOGY

Four human CoVs, that is, HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1, are usually low infectious and primarily infect upper respiratory tract with mild respiratory symptoms (common cold), whereas the other three human CoVs, that is, SARS-CoV, MERS-CoV, and 2019-nCOV, are zoonotic and highly infectious, and predominantly cause severe lower respiratory tract infection which could rapidly

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progress to pneumonia, and have been categorized as major public health threats[1-3,8,15,16]. The outbreak of SARS in 2002 in China resulted in 8098 cases and 774 deaths (case-fatality rate, 9.6%) in 37countries, and the outbreak of MERS in 2012 in Middle East Countries leading to 2494 cases and 858 deaths (case-fatality rate, 34%) in 27 countries[2]. As of February 24, 2020, 2019-nCoV has caused 77 262 cases and 2595 deaths in China, and 2069 cases and 23 deaths in the other 29 countries (total case-fatality rate, 3.3%)[15-17]. Hence, although 2019-nCoV can cause a severe respiratory disease like SARS and MERS, it was less pathogenic than SARS-CoV, and much less than MERS-CoV. However, the number of 2019-nCoV infected patients in first two months were nearly 10 times of that of SARS patients totally, which implicated that 2019-nCoV was more transmissible than SARS-CoV and MERS- CoV[16].

Human CoVs primarily spread by virus-containing droplets or aerosols expelled by infected individuals when patients cough, talk loudly or sneeze. Direct contact with virus-contaminated fomites is also a route of human CoVs transmission[4,8,18]. Recently, SARS-CoV, MERS-CoV and 2019-nCOV have also been detected in stool samples from patients by RT-PCR assay, and been isolated from the mucous membranes of gastrointestinal tract in a few cases[19]. Hence, fecal-oral route may also be a route of transmission for SARS-CoV, MERS-CoV and 2019-nCOV.

The conjunctiva of the eye is easily exposed to infectious droplets and fomites during close contact with infected individuals and contaminated hands. Hence, conjunctiva is postulated to be an important portal of entry for respiratory and enteric viruses, while tear and conjunctival secretions may contain virus and spread viral infection[4]. Some respiratory virus such as human adenovirus (species D) and avian influenza virus (H7), and a few enteric viruses including enterovirus 70, can cause highly infectious conjunctivitis, or keratoconjunctivitis which could rapidly transmit by direct contact with contaminated hands[4]. However, the role of eye in the transmission of human CoVs is still controversial which will be discussed in the context.

CLINICAL MENIFESTATIONS

The clinical features of 2019-nCoV disease (COVID-19) were similar to those of SARS and MERS, most patients presented with fever, dry cough, dyspnoea, and bilateral ground-glass opacities on chest CT scans[2,3,20-22]. However, COVID-19

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rarely resulted in notable symptoms of upper respiratory tract infection (e.g., rhinorrhoea, sneezing, or sore throat) which were commonly manifested in SARS and MERS, some COVID-19 patients were even manifested as no apparent respiratory symptoms at onset which never appeared in SARS and MERS[22,23]. Recent investigations also revealed that COVID-19 was occasionally manifested as enteric infection symptoms such as diarrhoea, whereas about 20%~25% of patients with MERS or SARS had diarrhoea[23]. More over, more than 80% of COVID-19 was manifested as mild or moderate pneumonia, and patients with severe COVID-19 mostly occurred in cases over 60 years and was accompanied by at least one underlying disorder, for example, cardiovascular disorders, diabetes, chronic obstructive pulmonary disease, and hypertension[22].

OPHTHALMIC MANIFESTATIONS

The conjunctiva can be infected by some respiratory viruses such as herpes virus, adenovirus and influenza virus, and a few enteric viruses such as enterovirus 70. Tears and conjunctival secretions from infected individuals may contain viruses and play as a medium of spread[4]. However, the eye is rarely involved in human CoVs infection. Until now, conjunctivitis has been reported only in five cases with 2019-nCoV infection, and in four cases with HCoV-NL63 infection, whereas no conjunctivitis or other ocular complications was confirmed in patients with SARS-CoV and MERS-CoV infection[4, 24-28].

Recently, human COVs RNA in tears and conjunctival secretions were tested by real time- polymerase chain reaction (RT-PCR) assay in patients with SARS-CoV and 2019-nCoV infection[4, 24-31]. Loon and colleagues detected SARS-CoV in tear samples from 36 consecutive SARS suspects (eight patients were confirmed later) by RT-PCR assay[29]. SARS-CoV was positive in only three of the eight SARS cases. Three patients with SARS-CoV positive in tears were sampled in the early phase of their illness (on Day 3, 4, and 9 after onset of fever, respectively), whereas the other five confirmed SARS cases with SARS-CoV negative results in tears were sampled in the later phase (mean 19.4 days) of their illness[29]. Nearly at the same time, Chan and colleagues reported their negative results of SARS-CoV testing in tear and conjunctival scraping samples from 20 probable SARS patients (17 patients were confirmed later) by RT-PCR and virus culture[30]. Among 17 confirmed SARS patients, 6, 8, and 3 cases were recruited during the first, second, and third week of

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their diseases, respectively. Neither SARS- CoV RNA were detected by RT-PCR, nor SARS-CoV isolated in virus culture in all tear and conjunctival scraping samples. Leong and colleagues detected SARS-CoV in 126 conjunctival specimens from 64 SARS patients in convalescent phase by RT-PCR, none of the patients had SARS-CoV detected in conjunctival samples[19].

On January 22, 2020, a Chinese respiratory specialist who visited Wuhan as a member of the national expert panel on pneumonia, claimed that he was infected by 2019-nCoV despite being fully gowned with protective suit and N95 respirator[31]. His first clinical manifestation was unilateral conjunctivitis, followed by fever and catarrhal symptoms two or three hours later. He postulated that 2019-nCoV probably first infected the conjunctiva, then spread and cause viral pneumonia[31]. Soon after his report, health care personnel in China were urged to use eye protection when they were in close contact with COVID-19 patients or suspects. However, Zhou and colleagues, in their preprint posted at medRxiv, reported that conjunctivitis was identified in only one patient out of 63 COVID-19 cases and 4 COVID-19 suspects[24]. Conjunctivitis was also the first symptom of 2019-nCOV infection in this patient. However, 2019-nCOV test by RT-PCR was positive and probable positive in conjunctival swab samples from only one and two COVID-19 cases without conjunctivitis, respectively. None of above three patients had ocular symptoms. 2019-nCOV RNA was not detected in conjunctival swab samples from the COVID-9 patient complicated by conjunctivitis, whom was an anesthesiologist. Her ocular symptoms occurred soon after performing tracheal intubation for a patient who was confirmed as COVID-19 later, followed by fever and cough. Unfortunately, personal protections used by this anesthesiologist were only surgical mask, cap, and gloves without gown, face shield or goggles during the tracheal intubation procedures. Her five colleagues were also infected by the same patient, yet none of them appeared any ocular complications [24].

More recently, two investigative groups from China simultaneously reported conjunctivitis in and 2019-nCOV RNA positive in conjunctival swab samples from COVID-19 patients[25,28]. Sun and colleagues, in their preprint posted at medRxiv, reported conjunctivitis in two patients out of 72 laboratory confirmed COVID-19 cases, however, 2019-nCOV was detected in conjunctival swab samples by RT-PCR only in one patient who was a nurse working in Emergency Department[25]. This patient presented with excessive tearing and redness in both eyes which were typical

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ocular manifestation of viral conjunctivitis, followed by a moderate fever of 38.2℃ one day later. 2019-nCOV RT-PCR test for the conjunctival and oropharyngeal swabs sampled 6 days after the onset of conjunctivitis was positive, but for those sampled 10, 19, and 21 days after the onset of conjunctivitis was all negative [25]. Xia and colleagues reported unilateral conjunctivitis in one patient out of 30 confirmed COVID-19 cases, conjunctival swabs sampled from this patient on 3 days and 5 days after the onset of COVID-19 were both positive for 2019-nCOV by RT-PCR, whereas 58 conjunctival swab samples from the other 29 COVID-19 patients were all negative for 2019-nCOV[28]. However, 2019-nCOV did not successfully isolated and cultured in the conjunctival swab samples from the COVID-19 patient complicated by conjunctivitis. More over, 55 of the 60 sputum samples from 30 COVID-19 cases showed positive PCR results for 2019-nCOV[28].

Although tears have been reported by the World Health Organization in 2003 to be one of the body fluids that might contain SARS-COV, the infectivity and clinical importance is still not understood[32]. Recent investigations have revealed that highly infectious human COVs (mainly SARS-CoV and 2019-nCOV) are rarely detected by RT-PCR, and never isolated by virus culture in tears and conjunctival secretions from SARS and COVID-19 patients[24-31,33]. Hence, it is hard to assess the infectiousness of tears and conjunctival secretions and their roles in virus spread.

The extremely low positive rate of human COV RNA test by RT-PCR in tears and conjunctival secretions from patients with SARS and COVID-19 may have several interpretations. Firstly, the sensitivity of RT-PCR test still needs to be improved. Previous reports about the sensitivity of RT-PCR in excretions ranged from 50% to 60%[30,34]. In current clinical practice, some 2019-nCOV suspects often had 2~3 repeated tests of nasopharyngeal swabs before the positive results were got[25]. The need remains for a highly sensitive and specific PCR test to diagnose human COV infections. Secondly, the samples were not collected at the right time. Recent evidence implicated that human COV RNA positive cases were all sampled in the early course of their illness, whereas human COV RNA negative cases sampled in the later or convalescent phase of their illness[30]. de Wit and colleagues demonstrated that, based on their rhesus macaque model study, MERS-CoV RNA could be detected in the conjunctiva only within 6 days post infection[35]. Hence, it is reasonable to postulate that human COV may present in tears only for a short period during the early phase of the disease. Thirdly, the contribution of antimicrobial agents in tears

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including lactoferrin and secretory IgA, and constant tear rinsing which continuously eliminating the virus on ocular surface into nasal cavity through nasolacrimal duct[34,37,38]. Lactoferrin can inhibit the binding of SARS-CoV to its entry receptor, angiotensin-converting enzyme 2 (ACE2), by preventing the attachment of SARS-CoV to heparan sulfate proteoglycans (HSPGs)[36]. Secretory IgA is another important antimicrobial agent in tears which helps to kill both bacteria and viruses. Host immune system can be activated and result in an evident increase in lactoferrin and secretory IgA levels in tears and circulating IgM level in plasm on the 3rd to 5th day, and circulating IgG level in plasm on the 10th to 15th day after CoV infection[36,37], which may explain why CoV RNA presents only in the early phase of the disease. Fourthly, the collection technique may not appropriate. World health organization highly recommends to use only synthetic fiber swabs with plastic shafts rather than calcium alginate swabs or swabs with wooden shafts for specimens sampling, as the latter two swabs may contain substances that inactivate some viruses and inhibit PCR testing[38]. Topical anaesthesia is also not recommended for tears and conjunctival scrapings sampling, for topical anaesthetic agent maybe also have negative influence on the viability of viruses[38]. More over, the volume of tears collected when sampling may also have some influence on the positivity of RT-PCR test. Fifthly,

MECHANISMS of TRANSMISSIOM by MUCOUS MEMBRANE MODE

Anatomically, the mucosa of ocular surface (conjunctiva and cornea) and upper respiratory tract is connected by nasolacrimal duct[4]. When dropped into the eye, liquid is partially absorbed by the cornea and conjunctiva, but mostly drained into nasal cavity through nasolacrimal duct, and then transferred towards the lower part of respiratory tract including nasopharynx and trachea, or swallowed into gastrointestinal tract[34]. This allows pathogens exposed to the eye to be transported to respiratory and gastrointestinal tract mucosa. More over, previous investigations have revealed that mucosa of ocular surface (conjunctiva and cornea) and respiratory tract share same receptors for some respiratory viruses[4,39-41]. For example, α-2-3-linked sialic acid (SA), the receptor of human adenovirus (species D) and avian influenza virus (H7), is highly expressed in conjunctival and corneal epithelia, and lower respiratory tract mucosa. Whereas α-2-6-linked SA, the receptor of human influenza virus, predominantly locates in conjunctival epithelia, as well as the nasal and tracheal mucosa[4]. ACE2, the entry receptor of 2019-nCoV, SARS-CoV and HCoV-NL63, is

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highly expressed on human lung alveolar epithelial cells, enterocytes of the small intestine and the proximal tubular cells of the kidney[4,39]. Positive expression of ACE2 was also detected in human conjunctival and corneal epithelial cells, however, ACE2 expression in human ocular surface is much less than in human lung and kidney tissues[40]. The binding capability of ACE2 protein on conjunctival epithelial cells to SARS-CoV spike protein is much lower than that on Vero E6 cells and that in lung tissues[41].

The efficacy of virus entry into host cells depends on three points: the invasiveness of the virus, viral receptors on host cell membrane, and immune conditions of the host. The virus binding to host cell membrane by its receptors is the first and key step for viral invasion. ACE2, a metallopeptidase, has been identified as the entry receptor of 2019-nCoV, SARS-CoV and HCoV-NL63, and is responsible for binding to spike protein on SARS-COV and HCoV-NL63 surface, and mediating SARS-CoV and HCoV-NL63 entry into host cells[4,11,39-42]. While MERS-CoV and most α-CoVs have been identified to utilize dipeptidyl peptidase 4 and aminopeptidase N as an entry receptor of their host cells, respectively[43]. Further investigations have revealed that the invasion of SARS-CoV and HCoV-NL63 into host cells not only relies on the presence of ACE2 on host cell membrane as an entry receptor, but also is modulated by other factors on host cell membrane, for example, HSPGs serving as attachment receptors[38,42,44].

The locations of viral entry receptor expression are consistent with the tissue tropism and pathogenesis of virus infection. At present, the mechanism of human CoVs invasion into host cells is still not clear. Lang and Milewska described the possible mechanism of ACE2-mediated host cell entry for SARS-CoV and HCoV-NL63 virus[36,42,44]. First, the virus docked and bound to host cells by the interaction between the spike protein on viral surface and heparan sulfate chains of HSPGs on host cell membrane. This action facilitated further binding of spike protein on viral surface to its entry receptor, ACE2, on host cell surface. Then, the binding of spike protein of the virus to ACE2 protein of host cell membrane triggered recruitment of clathrin, followed by clathrin-mediated dynamin dependent endocytosis of viral particles, which required actin cortex remodeling[37,42,44]. Considering 2019-nCOV has similar spike protein with SARS-CoV, it is postulated that 2019-nCOV also use

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ACE2 as its entry receptor to infect its host cells. Hence, it is reasonable to presume that 2019-nCOV shares same invasive strategy for host cell entry as SARS-CoV, and HSPGs may also work as attachment receptors during the entry of 2019-nCOV into its host cells.

INFECTION CONTROL and PERSONAL PROTECTION

Patients infected by 2019-nCoV, similar to SARS cases, mostly present with non-specific symptoms such as fever and dry cough, some of whom even with no evident symptoms, at the early phase of disease[9,16,21-24,45]. Hence, it is a challenging task for health care professionals in the northern hemisphere to early detect 2019-nCoV infection from influenza and other respiratory viral infections in the season of winter and spring when respiratory diseases frequently break out[45]. Hospital-related viral transmission especially transmissions between patients and health-care workers is frequently reported just before the outbreak of a highly infectious novel respiratory virus such as SARS-CoV and 2019-nCoV[8]. Previous investigations have revealed that patients infected by a novel virus never identified before can easily transmit the pathogen to health personnel without enough personal protection, the latter getting infected will further become a source of spread and soon cause hospital-related viral transmission[8,46-50]. In fact, 386 of 1755 patients (21.9%) and 8 deaths were health-care workers during SARS outbreak[46]. As of February 11, 2020, a total of 3019 medical health workers have been infected by 2019-nCoV in China, among whom 1716 cases were laboratory-confirmed COVID-19, and 5 cases passed away including an ophthalmologist named Wenliang Li, the whistleblower of 2019-nCoV infection in China[9,16].

At present, the physicochemical properties of 2019-nCoV is still not clear. Based on previous experience in SARS-CoV and MERS-COV infection control, it is postulated that 2019-nCoV is sensitive to ultraviolet irradiation and heating. It can be sterilized by heating at 56 °C for 30 minutes and by lipid solvents including 75% ethanol, chlorine containing disinfectant, peroxyacetic acid and chloroform, but not by chlorhexidine[47-49]. Many ophthalmic instruments, i.e., probes of A type and B type ultrasound, ocular contact lens such as Goldmann three-mirrored lens and gonioscope, trial frames, slit-lamp microscope, direct ophthalmoscope, automatic perimeter, and fundus camera, are frequently used by direct or close contact with patients, and may play as medium for virus spread. Non-contact tonometer may cause

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aerosol when measuring intraocular pressure by punching air onto the cornea of patients, hence it may also facilitate virus spread by aerosol transmission. Therefore, complete sterilization by 75% ethanol or hydrogen peroxide cleaning or immersion should be performed soon after each use of above ophthalmic instruments[47-49]. Complete sterilization using chlorine containing disinfectant, peroxyacetic acid, and hydrogen peroxide is mandatory for clinic and operating rooms. Hand washing preferably with the use of chlorhexidine alcoholic handrub after each ophthalmic examination or therapeutic procedure is highly recommended in the prevention of cross infection. Routine ophthalmic examinations such as slit-lamp examination and direct ophthalmoscopy are all performed by close contact, which means that the ophthalmologists are easily exposed to the droplets and tears or ocular secretions from, or to the ophthalmic instruments contaminated by confirmed patients or suspects with SARS, MERS, or COVID-19. Hence, strict hand hygiene and personal protection equipments including masks, gowns, gloves and goggles are highly recommended to avoid hospital-related viral transmission during ophthalmic practice[46-50].

When an ophthalmologist examines general ophthalmic outpatients, personal protection equipments including disposable caps, surgical mask and gown are highly recommended. When these patients are performed with high risk procedures, for example, direct ophthalmoscopy, lacrimal irrigation and probing, intraocular pressure measurement with noncontact tonometry, ophthalmic laser therapy, and ophthalmic surgeries, N95 respirator, gloves, and goggles or face shield, are strongly advised[47]. For patients with confirmed or suspect SARS, MERS, or COVID-19, any ophthalmic consultation should be completed within the quarantine ward to avoid cross-infection. Personal protective equipments including disposable caps, N95 respirator, goggles, face-shields, gloves, top and pants, and protective gowns should be worn all the time[48,50]. Moreover, hand washing, preferably with the use of chlorhexidine alcoholic handrub, and gloves changing after each high-risk procedure is mandatory to prevent cross-infection. Ophthalmic personnel are also recommended not to touch their goggle, face shield, surgical/N95 mask, eye, head, and neck region before hand washing procedure is completed[48,50].

Nonurgent ophthalmic operations and interventions, for example, cataract operations, ophthalmic plastic surgeries, squint extraocular muscle surgeries, intravitreal anti-VEGF injection, retinal photocoagulation, and YAG: Nd laser capsulotomy should be delayed if possible[47-50]. Ophthalmic emergencies such as

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acute angle-closure glaucoma and severe ocular injury should be operated immediately, and the operating theater is regarded as a high-risk area and proper personal protection equipments (i.e., disposable caps, N95 resporators, face shields, goggles, surgical gowns, and gloves) should be strictly practiced. When ophthalmic emergency surgeries are performed in patients with confirmed or suspect SARS, MERS, or COVID-19, personal protection equipments are similar to those for ophthalmic consultation of these patients. To avoid aerosol transmission during tracheal intubation, ophthalmic local anaesthesia is highly recommended than general anaesthesia, and patiemts should wear N95 respirators during ophthalmic surgeries under local anaesthesia[48,50].

CONCLUSION

The outbreak of SARS-CoV, MERS-CoV, and recently identified 2019-nCOV infection has become a world-wide health threat. Although respiratory droplets and direct contact have been identified as the main routes of transmission for above three highly infectious human CoVs, the role of the eye in transmitting human CoVs is still under discussion. Considering that the conjunctiva of the eye is directly exposed to infectious droplets and fomites during close contact with infected individuals and contaminated hands, and the mucosa of ocular surface and upper respiratory tract is connected by nasolacrimal duct and share certain entry receptors for some respiratory viruses. It is postulated that the eye may play three roles in human COVs infection. Firstly, it is the target organ for human COVs. Secondly, the conjunctiva may be a portal of entry for or transporter of human COVs to infect respiratory tract. Thirdly, tears and conjunctival secretions may be a medium to spread human COVs. However, the eye is rarely involved in SARS-CoV, MERS-CoV, and 2019- nCoV infection, conjunctivitis has been reported only in five cases with COVID-19, but never been confirmed in SARS and MERS patients, which suggesting that the eye is neither a preferred organ of human COVs infection, nor is a preferred gateway of entry for human COVs to infect respiratory tract.

Although it is quite rare, the possibility can not be excluded that pathogens exposed to the eye might be transported to nasal and nasopharyngeal mucosa by constant tear rinsing through lacrimal duct, and then cause respiratory tract infection, since mild to moderate symptomatic SARS can be developed in cynomolgus macaques model by nasal and conjunctival SARS-CoV inoculation, as that induced by nasal and bronchial

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SARS-CoV inoculation[4,51]. More over, the extremely low positive rate of huaman COV RNA test by RT-PCR in tears and conjunctival secretions from patients with SARS and COVID-19, may be related to the relatively low sensitivity of current RT-PCR technique, the later time for sample collecting, and the activation of host immune system and significant increase in lactoferrin and secretory IgA levels in tears and in circulating IgM and IgG levels in plasm. Hence, current negative RT-PCR results can not exclude the possibility of presence of SARS-CoV and 2019- nCoV in tears and conjunctival secretions. Considering close doctor-patient contact is quite common in ophthalmic practice which are apt to transmit human COVs by droplets and fomites, strict hand hygiene and proper personal protection are still highly recommended for health care workers to avoid hospital-related viral transmission during ophthalmic practice.

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Declarations

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Not applicable.

Consent for publication

Not applicable.

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Authors' contributions

Sun CB and Liu Z, performed the majority of the writing; Sun CB, Wang YY and Liu GH performed literature review and data collection; Liu Z and Sun CB revised the manuscript.

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