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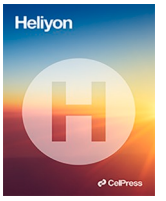

Research article

Presence of CoV-2 antibody in vitreous humor after Cov-2 infection

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ABSTRACT

Purpose: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a life-threatening disease with largely unknown intraocular pathogenesis. Herein, we determined the presence of SARS-CoV-2-specific ribonucleic acid (RNA) and virus-associated antibodies in the vitreous humor of people who have recently recovered from SARS-CoV-2 infection.

Design: This cross-sectional study included 33 patients (33 eyes) who have recently recovered from SARS-CoV-2 infection. Vitreous humor and blood serum samples were tested for the SARS-CoV-2 RNA and virus-associated antibodies.

Results: Among 33 participants, blood serum and vitreous humor were all tested negative for SARS-CoV-2 RNA. SARS-CoV-2-specific IgM was detected in 87.88 % (29/33) patients in blood serum and 6.10 % (2/33) in vitreous humor; SARS-CoV-2-specific IgG was detected in 96.97 % (32/33) patient in blood serum and 81.82 % (27/33) in vitreous humor. Statistical significance was found for IgM expression between blood serum and vitreous humor ($P < 0.01$), while IgG was not ($P = 0.11$). The days after recovery were statistically longer both in IgM-positive blood serum samples group and IgG-positive vitreous humor samples group compared with negative samples of each group ($P < 0.01$). Additionally, no statistical difference could be detected in antibody expression in vitreous humor between different groups divided on the condition of the risk of blood-retina-barrier (BRB) failure ($P = 0.49$ for IgM; $P = 0.37$ for IgG).

Conclusion: After recovering from COVID-19, no SARS-CoV-2 RNA was detected in vitreous humor, but anti-CoV-2 IgM was detected in 6.1 % and IgG in approximately 80 % of vitreous humor samples of participants. We also found that the positivety rate of SARS-CoV-2-specific antibodies in the blood serum and vitreous humor were both correlated with the days after recovery since the infection.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a significant

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impact on global health as it has disrupted many livelihoods since Dec 2019. Early reports described COVID-19 as a respiratory disease. However, multi-system injuries, including the central nervous system and eyes, have been widely reported [1,2]. Studies have shown that the virus can infect ocular tissues and manifest as conjunctivitis in 6%–66 % of patients [3].

SARS-CoV-2 could transmit through mucous membranes in both the respiratory system and ocular surface by binding to the angiotension-converting-enzyme-2 (ACE2) [4]. Several studies have reported the presence of viral RNA in tears, conjunctival swabs, and conjunctival secretions of COVID-19 patients [5,6]. These findings suggest that the virus can replicate in ocular tissues and potentially transmit through ocular secretions. Additionally, SARS-CoV-2 antigens have been detected in the retina and optic nerve of deceased COVID-19 patients [7]. These results indicated that the virus could also invade deeper ocular structures. A recent study also detected the SARS-CoV-2 viral RNA in around 19 % of asymptomatic individuals with SARS-CoV-2 infection in aqueous humor [8].

To date, most studies on the expression of viruses and virus-associated antibodies in the retina and vitreous cavity were conducted in postmortem ocular tissues, which cannot reflect the intraocular status of the normal population recovered from infection. We aim to try to detect the presence and persistence of living virus and virus-associated antibodies in general population, who were patients diagnosed with common retinal and vitreous diseases with no COVID-19 associated ocular manifestations in need of surgical treatment.Herein, we assessed the viral RNA and virus-associated antibodies expression in patients who have recovered from recent COVID-19 infection and have no SARS-CoV-2-related retinopathy such as retinal artery occlusion (RAO), retinal vein occlusion (RVO), paracentral acute middle maculopathy (PAMM) and acute macular neuroretinopathy (AMN) [9], in order to better understand the potential impact of COVID-19 on the visual system in general population (people with history of COVID 19 infection yet were otherwise healthy).

2. Materials and methods

This cross-sectional study was approved by the Medical Ethics Committee of Zhongshan Ophthalmic Center (approval No.2023KYPJ011) and adhered to the principles of the Declaration of Helsinki. Corresponding informed consent was obtained from each patient.

Participants:A total of 33 patients (33 eyes) undergoing posterior pars plana vitrectomy (PPV) in Zhongshan Ophthalmic Center from Feb 3, 2023 to Feb 24, 2023 were included in this study.

Inclusion Criteria:Participants were distinctively diagnosed with monocular macular hole (MH), epiretinal membrane (ERM), rhegmatogenous retinal detachment (RRD), and proliferative diabetic retinopathy (PDR) with no known SARS-CoV-2 related retinopathy confirmed by color fundus photograph (CFP) and optical coherence tomography (OCT). All patients had a confirmed COVID-19 infection history within 3 months based on nasal swab SARS-CoV-2 PCR testing and had recovered from the infection, as confirmed by negative nasal swab SARS-CoV-2 antigen testing within 24 h before the ocular surgery.

Exclusion Criteria:Patients with previous PPV history, severe vitreous hemorrhage, or other forms of severe ocular opacity that made it difficult to visualize the optic nerve head during surgery were excluded. Patients with exsisting COVID-19-related symptoms, such as cough, fever, shortness of breath, loss of taste and/or smell, eye redness, eye pain, or eye soreness were also excluded from the study.

Questionnaire:A questionnaire was carried out on the same day of the surgery to collect detailed information about the COVID-19 infection, including the exact date tested positive and negative for SARS-CoV-2 during the course of infection,and symptoms they experienced. The date data were all supported by SARS-CoV-2 RNA or antigen testing results. History of immune diseases including primary immune deficiency, acquired immune deficiency, allergic reaction and autoimmune disease etc, history of immunotherapy including activation immunotherapies and suppression immunotherapies, history of 2019-nCoV vaccine and history of intravitreal injection of antiviral treatments were also gathered.

SARS-CoV-2 Testing: On the surgery day, blood serum samples (1 ml) from 33 participants were collected, processed and stored at 4 °C at the State Key Laboratory of Ophthalmology of Zhongshan Ophthalmic Centre.Vitreous humor samples (0.2 ml) from 33 eyes were collected at the beginning of posterior pars plana vitrectomy (PPV) using the deep vitreous biopsy technique by the method previously described by Vivek Pravin Dave et al.[10]. The samples were tested for SARS-CoV-2 RNA using the Real-time quantitative polymerase chain reaction (RT-PCR, qPCR) technique utilizing specifically designed primers targeting the ORF1ab and N genes of the SARS-CoV-2 and the primer sequences were listed in Table 1. The procedure is carried out according to the instructions described in the manufacture book of the testing kit(BioGerm Corp., Shanghai, China). In addition, colloidal gold immunochromatographic assay (GICA) was used to detect the SARS-CoV-2-specific antibodies, including IgM and IgG (threshold value of which are 1 ng/ml for both antibodies). The test is carried out according to the procedure described in the manufacture book of the testing kit （BEIJING GIANTMED MEDICAL DIAGNOSTICS LAB, Beijing, China）. Prior to our formal commencement of the research, the false positive rate of the IgM and IgG testing kit was also determined by enrolling participants with no history of infection. The blood and vitreous humor

Table 1
The Primers of SARS-CoV-2 RNA PCR detection.

Target	Forward/Reverse Primer (5′-3′)
ORF1ab gene	CCCTGTGGGTTTTACACTTAA /ACGATTGTGCATCAGCTGA
N gene	GGGGAACTTCTCCTGCTAGAAT /CAGACATTTTGCTCTCAAGCTG

were collected from 14 participants (15 eyes in total; 8 with endophthalmites, 3 with vitreous hemorrhage (VH), 3 with RRD, and 1 with uveitis) with no history of COVID-19 infection and were tested for Covid-19-specific RNA, IgM as well as IgG. All samples were tested negative, adding to the reliability of this method.

2.1. Statistical analysis

Data analyses were performed applying SPSS version 26.0 (IBM Corp., Armonk, NY.). Continuous variables were displayed as the mean ± standard deviation ($\bar{x}$ ±SD) or the median with an interquartile range (IQR) (25 %, 75 %), and categorical variables were presented as percentages (%). The Kolmogorov–Smirnov (K–S) method is used for normality test. The Wilcoxon rank sum test was used for comparison between non-normally distributed variables between groups. Categorical variables were displayed as percentages and compared between groups using the Chi-square test and Fisher exact test.

3. Results

Participants distribution: A total of 33 participants were included in this study and the enrollment process was displayed in Fig. 1. Among them, 18 (54.5 %) were male, and the median age was 55 (range:33–67; IQR: 50.0,60.5) years old. All participants were distinctively diagnosed with MH (4, 12.1 %), ERM (11, 33.3 %), RRD (12, 36.4 %), and PDR (6, 18.2 %). The basic characteritics for participants was shown in Table 2.

Systemic and Eye symptoms:Of all 33 participants, 33/33 (100.0 %) had experienced fever (temperature higher than 37.3 °C) as well as headache, 32/33 (97.0 %) had experienced coughing during the infection.As for eye symptioms, 8/33 (24.2 %) had some, including eye soreness 5/33 (15.2 %), eye pain 3/33 (9.1 %), blurry vision 2/33 (6.1 %) and eye redness 1/33 (3.0 %) during the course of infection.

SARS-CoV-2 detection: Confirmation of COVID-19 infection and recovery was done as was shown in Table 3. No COVID-19-specific RNA was detected in either blood serum or vitreous humor. Of all 33 participants, 29 of 33 (87.9 %) had anti-SARS-CoV-2 IgM in their blood serum while 32 of 33 (97.0 %) had IgG. In vitreous humor, 2 of 33 (6.1 %) samples were positive for anti-SARS-CoV-2 IgM and 27 of 33 (81.81 %) for IgG. The distribution of SARS-CoV-2 IgM antibody was different between blood serum and vitreous humor ($P < 0.01$), while IgG was not ($P = 0.11$) (Table 4). Moreover, the antibodies could only be detected in vitreous humor in the patients with positive blood serum CoV-2 antibodies for both IgG and IgM (Figs. 2 and 3).

The days after recovery:The days after recovery was defined as the number of days from the first day the patient recovered from the infection (defined as the first day a patient was tested negative for COVID-19 using nasal swab antigen test/SARS-CoV-2 PCR testing after infection), to the day the blood serum or vitreous humor samples were collected. The relationship between the days after recovery and types of antibodies was analyzed and shown in Table 5 and Fig. 4. The days after recovery in the positive group was numerically shorter than that in the negative group regardless of the antibody and sample types. Statistical differences could be detected for the IgM in blood serum IgM and IgG vitreous humor. In groups with insufficient sample abundance, the same trend could also be noticed.

As antibodies were originally generated from immune systems and stayed in blood as long as the blood-retinal barrier (BRB) remained unattacked, we aim to analyze whether BRB failure could influence the presence of antibodies in vitreous humor. All 33 patients were divided into 2 groups based on the risk of BRB failure. Diseases as MH and ERM have no vitreous or retina hemorrhage, and the retinal pigment epithelial (RPE) remain unchanged, suggesting the completeness of both inner and outer layer of BRB. However, RRD usually has pigment particles in vitreous fluid, indicating the damage of RPE, and PDR usually has hemorrhage of retina, meaning the damage of retina vessels, presenting as evidence of BRB damage [11,12]. Group H had a higher risk of BRB failure and consisted of patients with PDR and RRD. Group L had a lower risk of BRB failure and consisted of patients with ERM and MH. No difference could be detected for the ratio of both positive IgM($P = 0.49$) and IgG ($P = 0.37$) between group H and group L. The results were displayed in Tables 6–8.

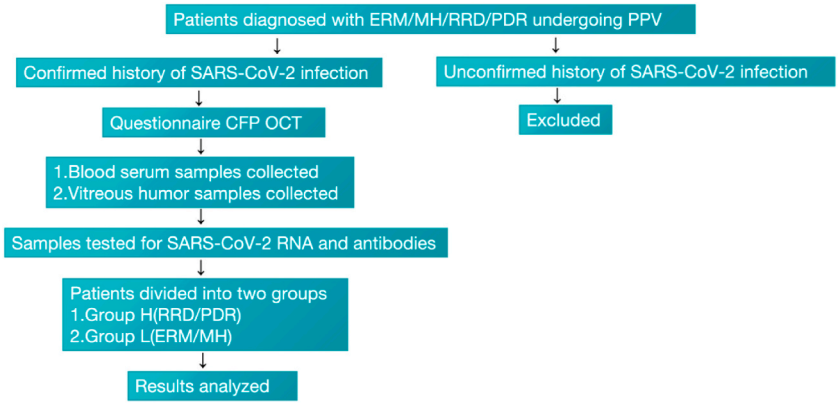

Fig. 1. Patients enrollement process.

Table 2
The basic characteristics for participants.

Characteristics	Values
Number of participants	33
Age ($\bar{x}$ ±SD)	54.24 ± 8.92
Gender (male,n,n/N%)	18,54.5 %
History of immune diseases (n,n/N%)	0,0.00 %
History of immunotherapy (n,n/N%)	0,0.00 %
History of vaccination (n,n/N%)	33,100.00 %
History of antiviral treatments (n,n/N%)	0,0.00 %

*The number of positive participants is defined as n , the number of total participants is defined as N.
*History of immune diseases include primary immune deficiency, acquired immune deficiency, allergic reaction, autoimmune disease etc.
*History of immunotherapy include activation immunotherapies and suppression immunotherapies.
*History of vaccination is refferred to 2019-nCoV vaccine.
*History of antiviral treatments is defined as intravitreal injection of antiviral drugs such as Ganciclovir (GCV).

Table 3
The preoperativel nasal swab SARS-CoV-2 PCR or antigen tests results.

	History of infection	Confirmation of recovery
Method	SARS-CoV-2 PCR tests	SARS-CoV-2 antigen tests
Results	Positive, 33/33, 100.00 %	Negative, 33/33, 100.00 %

Table 4
The detection rate of SARS-CoV-2 RNA and antibody in blood serum and vitreous humor.

	Blood serum (n/N,%)	Vitreous humor (n/N , %)	P
RNA	0/33 , 0.00 %	0/33 , 0.00 %	
IgM	29/33 , 87.90 %	2/33 , 6.10 %	<0.01
IgG	32/33 , 97.00 %	27/33 , 81.81 %	0.11

*The number of positive samples is defined as n , the number of total samples is defined as N.

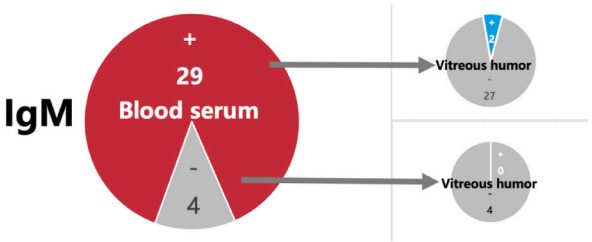

Fig. 2. IgM could only be detected in vitreous humor as long as it being detected in blood serum.

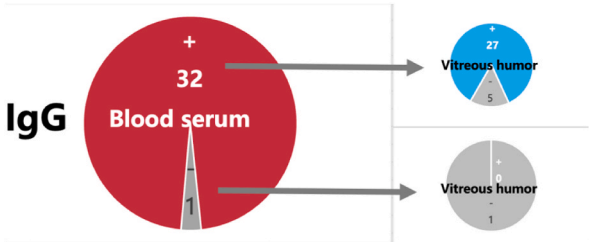

Fig. 3. IgG could only be detected in vitreous humor as long as it being detected in blood serum.

Table 5
The days after recovery in relation to the types of antibodies.

	results	n	Blood serum	*P*	n	Vitreous humor	*P*
			days			days	
IgM	+	29	46.45 ± 12.68	0.01	2	19.5 ± 0.71	–
	–	4	62.75 ± 7.46		31	50.7 ± 10.18	
IgG	+	32	47.94 ± 13.14	–	27	46.2 ± 11.76	0.008
	–	1	64 . 00		6	60.67 ± 8.19	

*The number of samples is defined as n.

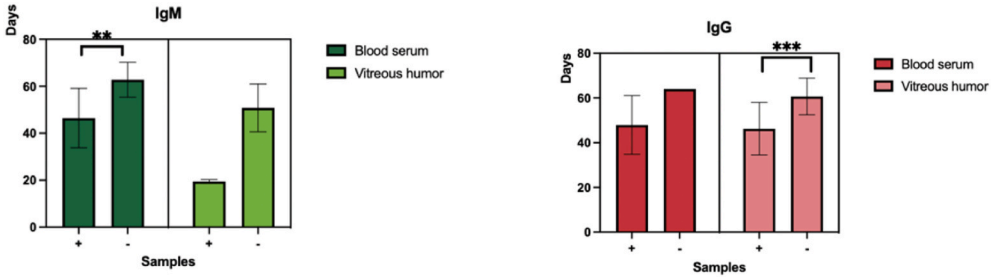

Fig. 4. 1 The days after recovery in relation to IgM, 2 The days after recovery in relation to IgG.

4. Discussion

Although several studies have already reported the detection of positive CoV-2 RNA in the vitreous humor of post-mortem individuals who died from COVID-19, it still remains unknown whether the SARS-CoV-2 virus exists in the vitreous humor [8] and how long it can persist in a generally infected population. In this study, we detected the SARS-CoV-2 RNA and related antibodies in living individuals recovering from recent COVID-19 infection for the first time.

Even the eye is an immune privileged organ, viral persistence has been reported in the anterior segment of the eye in the asymptomatic carrier and recovered patient [8]. KOO et al. [8] reported the presence of CoV-2 RNA in anterior humor in individuals with no virus-related symptoms and negative nasal swab CoV-2 RNA testing. However, in our study, no CoV-2 RNA could be detected from the vitreous humor, even in patients only 12 days after the infection. The difference could be due to the toxicity between the ancestral strain and the Omicron strain as the latter was the predominant strain during the detection period of our study in China. Another possible reason could be the enhanced immune privilege property of the vitreous cavity.

As an immune-privileged site, the blood-ocular barrier isolates the eye from the systemic immune system. The presence of vitreous antibodies is considered evidence of primary ocular infection or the breakdown of BRB. Van Gelder RN et al. [13] detected the HSV or CMV virus antibodies in the vitreous humor of patients. There are also minimal reports of the positive anti-CoV2 antibody in aqueous or vitreous humor in post-mortem patients [9]. Nevertheless, until recently, there was a definite lack of knowledge regarding the intraocular presence and duration of anti-CoV2 antibodies in vitreous humor after COVID-19 infection. To the best of our knowledge, this is the first study to analyze the anti-CoV2 antibody in intraocular fluid in living individuals after the COVID-19 infection.

In this study, 81.81 % of patients tested positive for anti-COV-2 IgG, and 6.1 % tested positive for IgM in vitreous humor. These results suggest that a significant proportion of individuals who recovered from COVID-19 have the IgG expression in the vitreous humor for up to 67 days. The presence of antibodies in vitreous humor was only detected in patients with positive blood antibodies, suggesting that the existence of antibodies in the blood is the prerequisite for their detection in vitreous humor. The detection rate of IgM in blood was significantly higher than that in the vitreous humor, and the duration of IgM in blood was longer, which is possibly due to the relatively large size of IgM affecting its transmission into the eye. The negative groups for IgG and IgM in both vitreous humor and blood serum had a longer recovery time, suggesting that the titer of antibodies may gradually decrease with time. The presence of IgG and IgM in intraocular fluid may have a protective effect against secondary infection.

In this study, we also investigated the relationship between BRB damage and the detection of vitreous antibodies. ERM and MH were considered chronic retinal diseases with very limited BRB damage. Previously we have performed fundus fluorescein angiography (FFA) or optical coherence tomography angiography (OCTA) in 5 patients with ERM or MH and found no retinal vascular leakage. However, positive anti-CoV-2 antibodies could also be found in patients with ERM and MH. There was no statistical difference in the detection rate of vitreous antibodies between different diseases. These results suggest that disease type may not be relevant for detecting vitreous antibodies, and BRB damage may not be the only factor contributing to its detection. Further studies are warranted to analyze the mechanism of CoV-2-specific antibodies in vitreous humor.

At present, posterior segment involvement has been described after COVID-19 in several studies [14]. Retinal macrovascular damage was the most common characteristic, including cotton wool spots, retinal hemorrhages, RVO, RAO and PAMM. Other potentially relevant manifestations include acute macular neuroretinopathy (AMN) and uveitis. The pathological mechanisms of

Table 6
Participants' involvement and distribution between Group H and Group L.

Groups	Group H		Group L	
Diagnosis	RRD	PDR	MH	ERM
n	12	6	4	11

*The number of samples is defined as n.Group H had a higher risk of BRB failure and consisted of PDR and RRD. Group L had a lower risk of BRB failure and consisted of ERM and MH.

Table 7
The types of diseases in relation to the distribution of SARS-Cov-2-specific IgM in vitreous humor.

	n1	n2	N	*P*
Group H	2	16	18	0.49
Group L	0	15	15	
N	2	31	33	

*The number of positive samples is defined as n1, the number of negative samples is defined as n2, the number of total samples is defined as N.Group H had a higher risk of BRB failure and consisted of PDR and RRD. Group L had a lower risk of BRB failure and consisted of ERM and MH.

Table 8
The types of diseases in relation to the distribution of SARS-Cov-2-specific IgG in vitreous humor.

	n1	n2	N	*P*
Group H	16	2	18	0.37
Group L	11	4	15	
N	27	6	33	

*The number of positive samples is defined as n1, the number of negative samples is defined as n2, the number of total samples is defined as N.Group H had a higher risk of BRB failure and consisted of PDR and RRD. Group L had a lower risk of BRB failure and consisted of ERM and MH.

COVID-19-associated posterior segment diseases are still unclear, but they are speculated for the following reasons: 1) directed infection, 2) immune response, and 3) coagulation abnormalities and thrombogenesis. Our study revealed the presence of a CoV-2 antibodies in vitreous humor, which may provide a possible explanation for the COVID-19-associated posterior segment diseases.

The main limitations of this study included the small sample size,which may increase selection bias, Type II errors and such. Our findings about SARS-CoV-2 RNA and antibodies in vitreous humor should be validated in a larger population. Moreover, this study is a cross-sectional study. A follow-up study is needed to analyze the vitreous viral RNA and antibodies at different time points to understand the immune response dynamics in the eye. Last but not least, because of the technical limitation, current methods for the detection of Covid-19-specific antibodies both in blood and in vitreous humor are only possible to distinguish positive results from negative results. Thus the Goldmann-Witmer (G-W) coefficient is uncalculatable in this study. Since the G-W coefficient is the key to determine whether the antibody is locally produced or passive leakage from the blood due to the systemic infection, further research should be carried out for quantitive analysis of COVID-19-specific antibodies in blood and vitreous humor.

Our results provide data of RNA and antibodies in intraocular fluid after COVID 19 infection, the expression of virus-associated antibodies may be related with ocular complications of COVID19 and antibody level in intraocular fluid may be a protective factor for eyes when the upcoming waves of SARS-CoV-2 infection attack.

5. Conclusion

In conclusion, our study detected the SARS-CoV-2 RNA and related antibodies in living individuals recovering from recent COVID-19 infection for the first time and found no SARS-CoV-2 RNA but positive anti-CoV-2 IgG in aproxiemately 80 % vitreous humor samples. These findings provided novel insights into the detection of CoV-2 infection and immune response in the posterior segment of eye, contributing to a better understanding of the potential impact of SARS-CoV-2 on the visual system.

Ethics statement

Written informed consent was obtained for anonymized patient information to be published in this article.

Data availability statements

The data that support the findings of this study are available from the corresponding author, [A H], upon reasonable request.

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CRediT authorship contribution statement

Yuntong Li: Writing – original draft, Formal analysis. **Jiaqing Li:** Investigation. **Songshan Li:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Zhengjie Xu:** Writing – review & editing. **Wei Ma:** Investigation. **Xinyan Wu:** Software, Resources. **Yayi Yan:** Software, Resources. **Ying Wang:** Software, Resources. **Andina Hu:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Andina Hu reports financial support was provided by National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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