

# Lactoferrin for the treatment of COVID-19 (Review)

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Received June 15, 2020; Accepted September 25, 2020

DOI: 10.3892/etm.2020.9402

**Abstract.** The coronavirus disease 2019 (COVID-19) outbreak was caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical outcomes of elderly individuals and those with underlying diseases affected by COVID-19 are serious, and may result in acute respiratory distress syndrome (ARDS) and even mortality. Currently, the clinical treatments for COVID-19 mostly involve symptom alleviation measures and non-specific broad spectrum antiviral drugs, as highly effective antiviral drugs and vaccines are not yet available. Lactoferrin (LF) is a safe iron-binding glycoprotein that is present in the milk of the majority of mammals and exhibits broad-spectrum antiviral activity, including against coronaviruses. In addition, LF also exhibits anti-inflammatory, anti-infective and immune-regulating properties, which are in line with the treatment requirements for SARS-CoV-2 infection. Therefore, the use of LF may be of value in the prevention and/or management of COVID-19. The aim of the present review was to summarize the previous reports on the antiviral properties of LF and compare these with the characteristics of SARS-CoV-2 infection, in order to determine whether LF could be used to assist in the prevention of COVID-19 and to investigate the possible underlying mechanisms governing its mode of action.

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## 1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel  $\beta$ -coronavirus, which has caused an ongoing outbreak of atypical pneumonia worldwide. According to official data from the World Health Organization (1), by October 7, 2020, >35,347,404 people have been affected by the SARS-CoV-2, and >1,039,406 patients had succumbed to the disease. A number of countries have required that residents reduce social activities and self-quarantine to limit the spread of coronavirus disease 2019 (COVID-19), which has caused major changes and disruptions to daily life, including work, school, sports, events and social activities (2,3). During the mandatory isolation, it is crucial to maintain mental and physical health through physical exercise (4,5). The clinical manifestations of COVID-19 are non-specific and range from asymptomatic infection to severe respiratory failure. The most common symptoms of COVID-19 include cough, fever and dyspnea (6). Elderly individuals and those with underlying conditions, such as cardiovascular and lung diseases, may suffer from more severe symptoms and mortality (7). Obesity has also been identified as a risk factor for the disease (8). Environmental factors, social customs and epidemic-specific attitudes, administrative issues and other factors will all have a major impact on the prevalence of COVID-19 (9).

The pathogen of COVID-19, SARS-CoV-2, is a positive-sense single-stranded RNA virus of the  $\beta$ -coronavirus genus (10,11). SARS-CoV-2 has been demonstrated to have a spherical morphology with spike projections on the surface (12), and it shares a high sequence identity with severe acute respiratory syndrome coronavirus (SARS-CoV) (13). The spike S glycoprotein serves a major role in viral infections and is one of the main targets in the design of therapeutic drugs and vaccines (14). At present there is no specific therapeutic drug or vaccine for SARS-CoV-2 (15), so the drugs currently used are aimed at suppressing inflammation or improving

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**Key words:** lactoferrin, severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, receptors of host cells, immunomodulatory effects

symptoms. Some antiviral drugs appear to serve a positive role in treating COVID-19, particularly at the early phase, such as interferon, lopinavir, chloroquine/hydroxychloroquine and ribavirin (16). Traditional Chinese medicines, including Lianhuaqingwen, have also demonstrated beneficial outcomes when used to treat cases with mild symptoms (17). However, further clinical trials of drugs and vaccines for SARS-CoV-2 are required to assess their efficacy and safety. Fig. 1 presents the SARS-CoV-2 infection. SARS-CoV-2 can enter the host cell through the angiotensin-converting enzyme 2 (ACE2) site. Infected individuals usually exhibit non-specific symptoms such as a cough and fever. Clinically, antiviral drugs are usually used for treatment, but there are no specific drugs and vaccines that are used.

Lactoferrin (LF), which is an iron-binding glycoprotein with a molecular weight in the range of 70-80 kDa, can transport iron in the blood and serum (18). LF is a simple polypeptide chain that is assembled into two symmetrical lobes (19). Each lobe contains two domains, which can bind a metal atom. It has been previously reported that the antiviral effect of LF is mediated by binding iron and is not affected by unsaturated iron levels (20). According to the available literature, the sequences and structures of LF from different sources (including from human, bovine and camel) are similar, except the N-terminal part of camel LF, as the first 50 residues of the N-terminus of camel LF shares less than 40% sequence identity with other sources of lactoferrin (21,22). LF is produced by mucosal epithelial cells in a number of different mammalian and fish species, and is found in mucosal secretions, bodily fluids and secondary neutrophil granules (23).

After LF is successfully isolated and purified, a number of its physiological activities have been gradually uncovered, including antifungal, antiviral and anti-inflammatory activities, as well as effects on the immune response (18,24,25). These activities are mediated through the capacity of LF to bind iron and to interact with components of the host and the pathogens (23). LF is positively charged *in vivo*, and can bind large molecules with negative charges, such as lipopolysaccharides and glycosaminoglycans, which is one of the key mechanisms underlying its antiviral activity (26). The protective effects of LF were first confirmed in 1987 in mice infected with the polycythemia-inducing strain of friend virus complex (27). LF has been identified to be effective against several viruses, which are listed in Table I (28-37).

COVID-19 is often characterized by an unusually long asymptomatic stage (3-14 days), while asymptomatic patients may be equally, if not more, contagious compared with symptomatic patients, which makes prevention extremely difficult, particularly during the flu season (38). The mechanism behind the asymptomatic stage may involve the fact that SARS-CoV-2 has developed an additional furin protease cleavage site in the spike protein (between the S1 and S2 domains), which enables the virus to infect and proliferate in large quantities in the nostril, salivary glands and throat, where furin protease and ACE2 are both expressed at high levels (39). Over a period of time, the virus proliferating in the upper respiratory tract can migrate to the lower respiratory tract and infect others via fluid droplets. If prophylactic measures are taken in time to reduce the virus load and/or prevent infection of other cells, the interpersonal infectivity and severity of later symptoms may be markedly reduced.

From the perspective of the SARS-CoV-2 infection process, preventing viral particles from entering the cells and interfering with endocytic pathways, preventing post-translational processing of multiple proteins, and targeting cell signaling pathways, are some of the approaches that can be used to identify effective therapies (11). In addition, due to the similarities between SARS-CoV-2 and SARS-CoV, drugs that have a therapeutic effect against SARS-CoV may also be considered as a possible treatment plan. The antiviral effect of LF is mediated through preventing the virus from binding to the target cell surface, which would be particularly effective during the early amplification phase of the virus in the salivary glands, throat and upper respiratory tract (40). LF has strong and extensive antiviral properties and therefore, it can be hypothesized the LF may be used as a potential drug for the treatment of COVID-19.

## 2. Two-stage interaction with receptors on host cells

To achieve infection, the virus must first attach to the host cell and then penetrate the cell membrane. There is a highly alkaline region near the N-terminal of LF, which may be combined with a variety of negatively charged macromolecules (41). This is an important basis for the antiviral activity of LF, as a variety of negatively charged macromolecules, such as glycosaminoglycans, often act as receptors on the surface of host cells that combine with viruses (42,43). It has been demonstrated that heparan sulfate proteoglycans (HSPGs) serve important roles in inhibiting human respiratory syncytial virus, Venezuelan equine encephalitis virus (44), Echovirus (45), herpes simplex virus (HSV), dengue virus (43) as well as other viruses (46).

Novel coronavirus is the pathogen of SARS. Its high infectivity, high mortality and low cure rates make it a major threat to public health (47). SARS-CoV is an enveloped, positive-strand RNA virus, composed of spike, envelope, membrane and nucleocapsid protein (48). SARS-CoV attaches to host cells by binding HSPGs (49), which are also the binding sites for LF on host cells (50). It has been demonstrated that LF can protect the host against a variety of viral infections by preventing the internalization of viruses, such as HSV, and by occupying their binding sites (51). The protective effects of LF against SARS-CoV Pseudovirus infection of 293E/ACE2-Myc cells has been investigated (31). It has also been demonstrated that HSPGs (binding sites facilitating SARS-CoV entry) are distributed on the host cell surface and LF occupies these binding sites to prevent the internalization of SARS-CoV and infection of host cells in the early stages. Therefore, LF may be useful as a potential therapeutic drug candidate for protecting host cells against SARS-CoV infections.

SARS-CoV-2 shares ~80% identity of the genome, similar receptor-binding domain (RBD) structures and cellular receptors (such as ACE2) with SARS-CoV (Fig. 2), and the  $\alpha$ 1 helix of the RBD binds to the peptidase domain (PD) of ACE2 via polar action (52). ACE2 has been demonstrated to be the primary receptor, while dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) is another controversial independent receptor of SARS-CoV-2 (53,54). DC-SIGN may be a factor that promotes ACE2-mediated infection (55). Although, to the best of our knowledge, there are no studies demonstrating that LF can

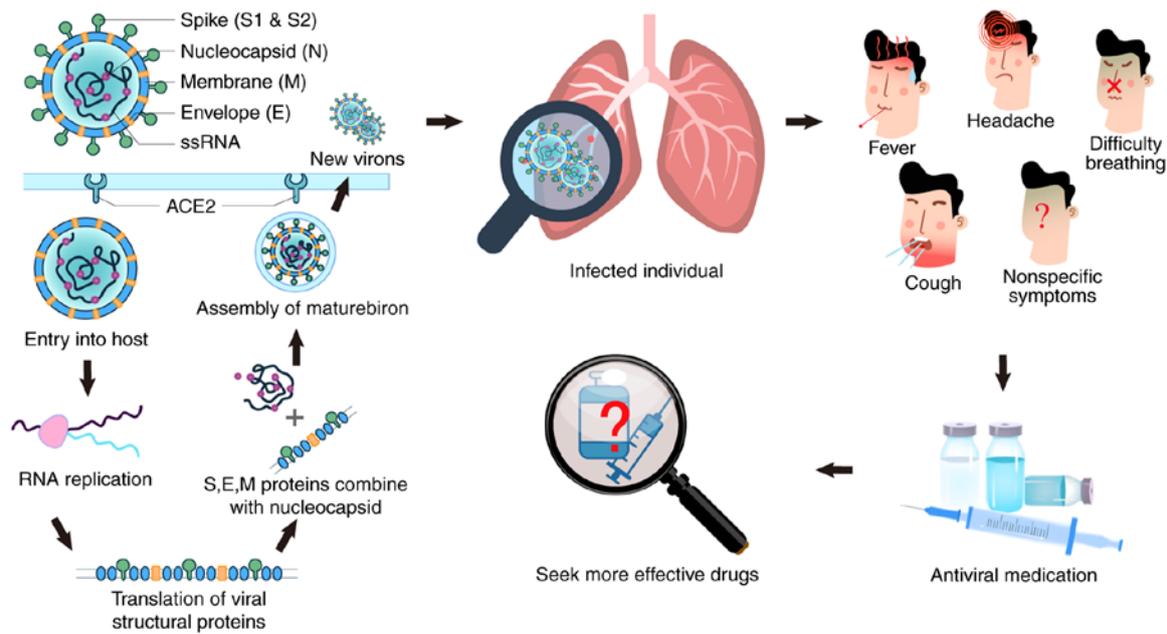


Figure 1. The SARS-CoV-2 infection. SARS-CoV-2 is composed of Spike, Nucleocapsid, Membrane, Envelope, and ssRNA. It binds to the ACE2 receptor on the surface of the host cell and enters the host cell. After a series of processes such as RNA replication and translation, it increases in value to obtain new virus. Infected individuals usually present with symptoms including a fever and headache. ssRNA, single-stranded RNA; ACE2, angiotensin-converting enzyme 2.

protect host cells by binding to ACE2, it has been demonstrated that LF can protect the host cell against dengue virus infection via binding to sites on the cell membrane, including DC-SIGN, heparan sulfate (HS) and low-density lipoprotein receptors (32). Therefore, it may be hypothesized that LF can also inhibit ACE2-mediated infection by binding to DC-SIGN. Fig. 2 presents the interactions between SARS-CoV-2-RBD and ACE2 (52).

In addition, it has been demonstrated that ACE2 is also abundantly expressed in gastrointestinal epithelial cells (56,57). Therefore, host cell internalization of SARS-CoV-2 may be identified in the gastrointestinal tract, and can lead to active infection and replication (13). Following oral administration, abundant LF remains on the lining of the gastrointestinal tract and protects host cells against infection by SARS-CoV-2 (18).

### 3. Immunomodulatory effects of LF

In addition to its interaction with host cells, LF can also enhance antiviral protection by modulating the immune response, such as enhancing phagocytosis and inducing apoptosis, among other functions (58). The immunomodulatory effects of LF have attracted attention as LF defends against infection and excessive inflammation, which is achieved through interaction with immune cells and cytokines (59). The immunomodulatory effects include i) enhancing the antigen expression ability of B cells and ii) regulating the function of T cells (60).

LF receptors (LFRs) are located on the surface of a variety of immune cells, such as various lymphocytes, macrophages and dendritic cells (61,62). LF can reduce the release of inflammatory factors by promoting the differentiation of CD4<sup>+</sup> T cells into Th1 cells (63). In addition, LF can stimulate neutrophil aggregation at the site of inflammation, activate phagocytosis by polymorphonuclear leukocytes and macrophages,

and increase the activity of natural killer (NK) cells. Oral administration of LF can enhance the killing activity of NK cells against tumor and virus-infected cells by facilitating the production of interleukin (IL)-18 (64). Furthermore, LF can increase the level of IL-12 in macrophagocytes, which triggers the migration of macrophages to inflammatory sites and activates CD4<sup>+</sup> T cells (59). On the other hand, cytokines are important for the immunomodulatory effects of LF. LF induces the expression of type I interferons (IFN- $\alpha/\beta$ ) and inhibits virus replication (58). IFN- $\alpha/\beta$  are known as potent antiviral cytokines and immunomodulators, which lead to the production of numerous antiviral bioactive compounds and cytokines (65). In summary, LF may be used as a natural immunomodulator for the treatment of COVID-19 (66).

### 4. Fusion between LF and the viral envelope

The virus infects host cells through fusion of its envelope with the host cell membrane, which is a key step during viral infection. It has been demonstrated that LF binds to the substances mediating the infection process on the virus envelope and inhibits fusion, thus preventing infection (67). The binding sites differ among different viruses. Hemagglutinin (HA) is the binding site on the H1N1 virus, and LF has been demonstrated to inhibit infection via fusion with HA (28). HA, which is a glycoprotein expressed in the virus envelope, is a key factor in the process of viral infection. Following LF binding to HA, the interaction and fusion between the glycoprotein on the virus surface and receptors on the host cell are inhibited, thereby preventing infection. In addition, LF inhibits respiratory syncytial virus (RSV), which is associated with a serious respiratory disease such as otitis media and lower respiratory tract involvement (LRTI) in infants (68), through fusion with the F protein on the virus envelope (27). LF binds to the F1

Table I. The antiviral activities of LF for some viruses.

Authors, year	Type of virus	Enveloped/naked	DNA/RNA	Sources of LF	Mechanism	(Refs.)
Oda <i>et al.</i> , 2020	Influenza A	Enveloped	RNA	Bovine	Interfering with the fusogenic function of viral hemagglutinin	(28)
Sano <i>et al.</i> , 2003	RSV	Enveloped	RNA	Human	Modulating RSV-induced IL-8 secretion and binding to RSV F protein	(29)
Pietrantonio <i>et al.</i> , 2003	Adenovirus	Naked	DNA	Bovine	Binding to the adenovirus penton base and competing with viral particles for cell membrane HS inserted in target cell membranes	(30)
Lang <i>et al.</i> , 2011	SARS-CoV	Enveloped	RNA	Bovine	Enhancing Natural killer cell activity and stimulating neutrophil aggregation and adhesion, binding to the heparan sulfate glycosaminoglycan (HSPG) and blocking the preliminary interaction between SARS-CoV and host cells	(31)
Chen <i>et al.</i> , 2017	Dengue Virus	Enveloped	RNA	Bovine	Interacting with Heparan Sulfate, Low-Density Lipoprotein Receptor and DC-SIGN	(32)
Weng <i>et al.</i> , 2005	Enterovirus 71	Naked	RNA	Bovine	Binding to viral protein 1 protein and host cells	(33)
Pietrantonio <i>et al.</i> , 2015	Toscana Virus	Enveloped	RNA	Bovine	Binding to Heparan Sulphate	(34)
Beljaars <i>et al.</i> , 2004	CMV	Enveloped	DNA	Human	Inhibition of CMV cell entry and indirect activities of lactoferrin on CMV infections via stimulation of the immune system	(35)
Ammendolia <i>et al.</i> , 2007	Herpes Simplex Virus type 1 (HSV-1)	Enveloped	DNA	Bovine	Competing with HSV-1 for heparan sulphate receptor on cell surface and affecting a post-entry step of viral infection by preventing VP-16 from being translocated to the nucleus	(36)
Ishikawa <i>et al.</i> , 2013	MNV	Naked	RNA	Bovine	Inducing the expression of anti-viral cytokine mRNA, such as IFN- $\alpha$ and IFN- $\beta$ , which are involved in the inhibition of MNV replication in the early phase of infection	(37)

RSV, Respiratory syncytial virus; IL, interleukin; HS, heparan sulfate; SARS-CoV, severe acute respiratory syndrome coronavirus; HSPG, heparan sulfate proteoglycans; DC-SIGN, dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin; CMV, cytomegalovirus; MNV, mouse norovirus; IFN, interferon.

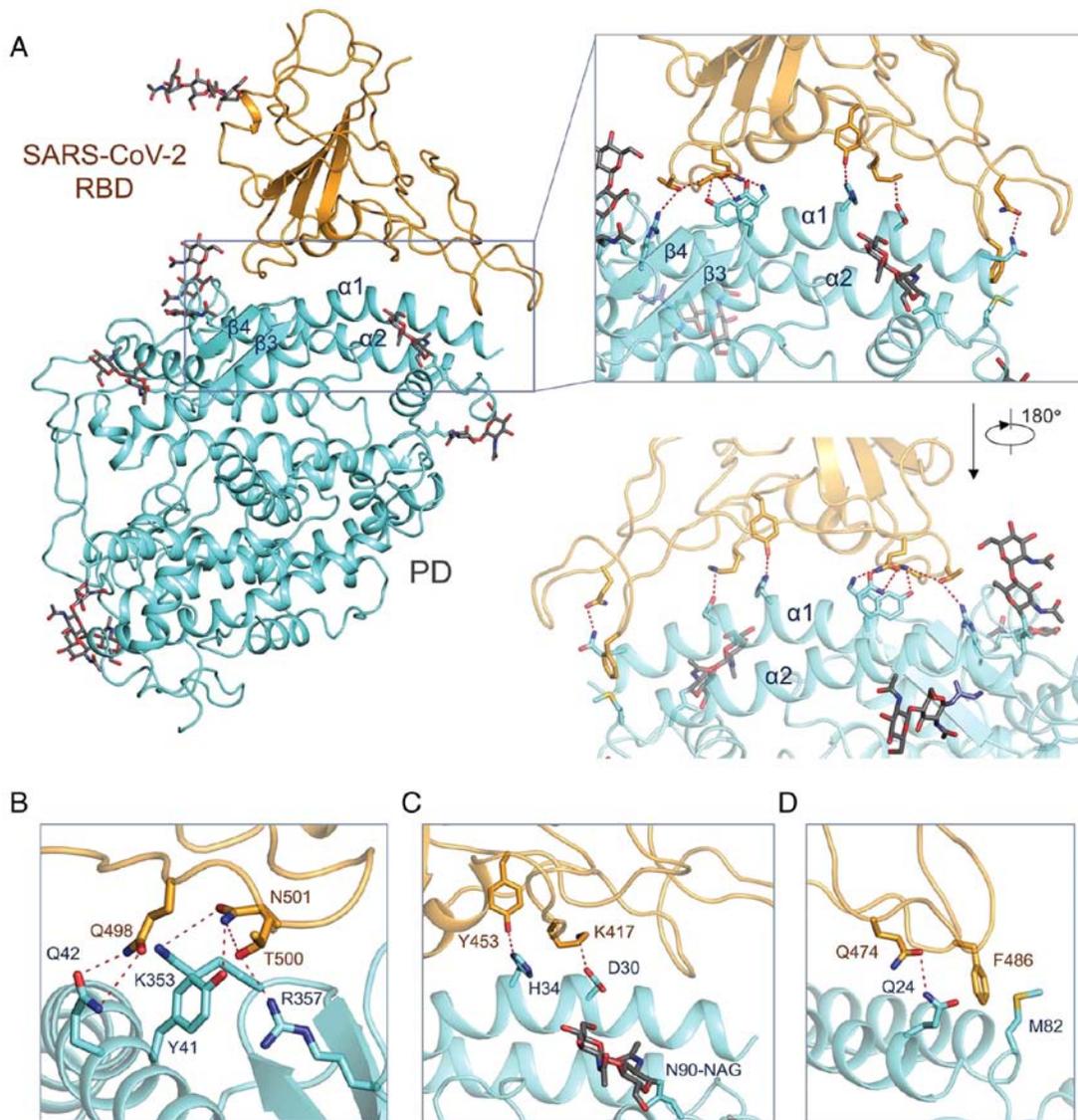


Figure 2. Interactions between SARS-CoV-2-RBD and ACE2. Yellow, the RBD of SARS-CoV-2; blue, the PD of ACE2. The red dotted line indicates the polar interaction. (A) The interaction between RBD and ACE2 is mainly through  $\alpha 1$  helix,  $\alpha 2$  helix,  $\beta 3$  and  $\beta 4$ . (B-D) The specific details of the interface. Reproduced with permission (52). NAG, N-acetylglucosamine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RBD, receptor-binding domain; ACE2, angiotensin-converting enzyme 2.

subunit of the F protein, thereby inhibiting the entry of RSV into epithelial cells, preventing the inflammatory response caused by RSV, and decreasing the infection of Hep-2 cells. LF protects the host cell against infection by adenovirus by specifically binding to its penton base (23). Overall, the protective activity of LF against viral infections is notable. However, whether LF is also effective in SARS-CoV-2 must be further investigated, and it is necessary to identify the binding sites on SARS-CoV-2.

## 5. Discussion and conclusion

The rapid spread of the SARS-CoV-2 pandemic has become a major global health concern. It is therefore urgent to develop effective therapeutic agents to prevent and treat SARS-CoV-2 infection. LF has exhibited extensive, broad-spectrum antiviral activity, indicating its potential for the treatment and prevention of SARS-CoV-2 (21,40). For example, LF treatment

on HSPGs and ACE2 can prevent SARS-CoV from infecting host cells (31), and LF has extensive immunoregulatory and anti-inflammatory effects (69,70), which may prove useful in the treatment of SARS-CoV-2 and the prevention of its devastating effects on multiple target organs. Furthermore, compared with other antiviral drugs, LF has a better safety profile. The use of LF may therefore hold promise in the treatment of COVID-19 and warrants further investigation.

However, there were certain limitations to the current review. The aforementioned possible effects of LF on SARS-CoV-2 are based on the effects of LF on other viruses, and there is currently a lack of direct research on the effects of LF on SARS-CoV-2. In addition, there remains certain problems in applying LF in the clinical setting. For example, it remains unknown which state of LF is more effective in treating SARS-CoV-2, namely unsaturated vs. saturated, human-derived vs. bovine-derived, whereas the combined metal, specific dosage and route of administration have yet

to be clearly determined, and these issues must be considered and resolved before applying LF in the clinical setting for the treatment of COVID-19.

In conclusion, the use of LF appears to be a promising approach to the treatment of COVID-19, but further investigations are required to verify its antiviral activity *in vitro* and *in vivo*.

### Acknowledgements

Not applicable.

### Funding

Liaoning Province Natural Science Foundation of China (grant no. 2020-BS-106).

### Availability of data and materials

Not applicable.

### Authors' contributions

YC, HW and MJ conceptualized the study. YW, PW, HW, YL, LW performed validation, research and reviewed the data. YW and PW wrote the manuscript. YW, PW, YC and MJ reviewed the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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