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REVIEW ARTICLE

The expression level of angiotensin-converting enzyme 2 determines the severity of COVID-19: lung and heart tissue as targets

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ABSTRACT

Researchers have reported some useful information about the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leading to CoV disease 2019 (COVID-19). Several studies have been performed in order to develop antiviral drugs, from which a few have been prescribed to patients. Also, several diagnostic tests have been designed to accelerate the process of identifying and treating COVID-19. It has been well-documented that the surface of host cells is covered by some receptors, known as angiotensin-converting enzyme 2 (ACE2), which mediates the binding and entry of CoV. After entering, the viral RNA interrupts the cell proliferation system to activate self-proliferation. However, having all the information about the outbreakof the SARS-COV-2, it is not still clear which factors determine the severity of lung and heart function impairment induced by COVID-19. A major step in exploring SARS-COV-2 pathogenesis is to determine the distribution of ACE2 in different tissues . In this review, the structure and origin of CoV, the role of ACE2 as a receptor of SARS-COV-2 on the surface of host cells, and the ACE2 distribution in different tissues with a focus on lung and cardiovascular system have been discussed. It was also revealed that acute and chronic cardiovascular diseases (CVDs) may result in the clinical severity of COVID-19. In conclusion, this review may provide useful information in developing some promising strategies to end up with a worldwide COVID-19 pandemic.

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1. Introduction

Severe acute respiratory syndrome (SARS)-CoV, as well as middle east respiratory syndrome (MERS) and SARS CoV 2 (SARS-CoV-2) belong to coronaviridae family (Payne, 2017; Schwartz & Graham, 2020). All these three viruses are pathogenic and cause of respiratory problems in humans (Kwok et al., 2019; Peeri et al., 2020). In the December 2019, a series of unexpected cases of pneumonia were observed in China (He, Deng, et al., 2020; Zu et al., 2020). The government and health researchers in this country proceeded strategies to control the outbreak of the virus and programmed an etiological study (Kucharski et al., 2020; Prem et al. 2020). Finlay, World Health Organization (WHO) announced that the SARS-CoV-2 causes the CoV disease 2019 (COVID-19) (Lai et al., 2020).

The COVID-19 incubation period is estimated from 1 to 14 days (Lauer et al., 2020; Linton et al., 2020). The lungs are the main organs that are affected by COVID-19 (Aigner et al., 2020; Cheng, Wang, et al., 2020), but in serious cases other parts of the body such as central nervous system (CNS) (Baig et al., 2020), kidney (Cheng, Luo, et al., 2020; He, Mok, et al., 2020), liver (Feng et al., 2020; Zhang, Shi, et al., 2020), heart (Akhmerov & Marban, 2020; Shi et al., 2020), stomach (Poggiali et al., 2020), intestine (Cao, 2020; Monteleone & Ardizzone, 2020; Turner et al., 2020) can also be affected.

Like many other respiratory diseases, the severity of the infection caused by the SARS-CoV-2 can vary from patient to patient. According to the latest findings, some cases of SARS-CoV-2 infection were associated with pneumonia and shortness of breath (Cao et al., 2020; Wu, Zhao, et al., 2020).On the other hand, some patients diagnosed with the SARS-CoV-2 showed developed respiratory failure, septic shock, or multiple organ failure (Landi et al. 2020; Liu et al., 2020). Notably, the fatality rate of infection was reported to be approximately 2% (Banerjee et al., 2020).

Scientists are trying to figure out the reasons for increasing rate of infection and death in infected population with the SARS-CoV-2 (Pedersen & Ho, 2020). The latest data from China are based on an analysis of confirmed cases, and generally show that elderly people and those who have already suffered from serious disease are significantly at higher risk of COVID-19 (Le Couteur et al., 2020; Lipsitch et al., 2020). The fatality rate of healthy people who die from COVID-19 is

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less than 1%, whereas the fatality rate for people with cardiovascular disease (CVDs) is more than 10% (Matsushita et al., 2020), for diabetics 7.3% (Hill et al., 2020), and for those with chronic respiratory disease is about 6% (Halpin et al., 2020).

Overall, less than 3% of COVID-19 cases showed fatal, and statistical analysis shows that 14.8% of these patients were older than 80 years (Le Couteur et al., 2020; Rothan & Byrareddy, 2020). These statistical analysis shows that older people are more prone to severe forms of COVID-19 (Le Couteur et al., 2020). The death had occurred in all age groups except in children and there were proportionally few cases among children in general. This pattern of increasing severity of the COVID-19 with age is totally different with the outbreak of some other CoVs. It is postulated that the severity of COVID-19 depends on a person's immune response and the type of infected organ (Rothan & Byrareddy, 2020).

2. Structure and origin of CoV

CoVs are single-stranded RNA viruses, sense-positive with animal origin and belong to the *Coronaviridae* family and the Nidovirales category (Chen et al., 2020; Pal et al., 2020). The CoVs are genotypically and serologically divided into four groups of α, β, γ, and δ. Approximately 30 species of CoV have been identified in vertebrates, whereas in human CoVs are dominantly from α and β groups (Zhou et al., 2020). CoVs belong to the group of β-CoVs and SARS-CoV-2 is the third known zoonotic CoV after SARS and MERS viruses, both of which also belong to the β-CoVs group (Boopathi et al., 2020).

Epidemiological studies of the early cases of SARS-CoV-2 pneumonia have shown that many cases have been exposed to the seafood market in Wuhan, China (Li, You, et al., 2020; Yang et al., 2020). It was also reported by WHO that SARS-CoV-2 was identified in specimens collected from the seafood market (Deng & Peng, 2020), but it was not yet fully understood what specific species of animals carry the SARS-CoV-2. SARS-CoV and MERS-CoV are known to be originated from bats as the main and natural reservoir and transmitted to humans from civet and camels, respectively (Jørgensen & das Neves, 2020).

It was recently confirmed that SARS-CoV-2 is a new CoV that is highly associated with bats' CoV (Chan et al., 2020). Moreover, it has been shown that the SARS-CoV-2 is a chimeric virus between the bat CoV and the CoV of unknown origin (Benvenuto et al., 2020; Ji et al., 2020). Recently, the RNA sequence similarity between the SARS-CoV-2 and the SARS-CoV was found to be about 80% (Wu, Wu, et al., 2020). In addition, a strong homology between SARS-CoV-2 and the bat CoV was reported. Thus, current evidence strongly confirms that the SARS-CoV-2 was originated from bats (Wu, Wu, et al., 2020; Zhou et al., 2020). Currently, SARS-CoV-2 has been isolated from pangolins, which shows 99% similarity to the strains isolated from humans infected with the SARS-CoV-2 (Wu, Wu, et al., 2020; Zhou et al., 2020). The origin of SARS-CoV-2 and the virus that trigged the outbreak of SARS in 2003 are generally related, however, the disease caused by each of these viruses is quite different (Peeri et al., 2020). The fatality rate of SARS is higher than COVID-19, but the prevalence of COVID-19 is much higher than that of SARS. Since 2003, there has been no outbreak of SARS-CoV anywhere in the world (Peeri et al., 2020).

3. The role of ACE2

One of the many factors involved in the development of high blood pressure and atherosclerosis is the renin-angiotensin system (RAS) (Battistoni & Volpe, 2020). Activation of RAS by the production of angiotensin (II) causes functional changes in the cardiovascular system (Masi et al., 2019). These changes include left ventricular hypertrophy, increased perforation of the smooth muscle of the vascular wall, and impaired vascular endothelial function (Ageev et al., 2008). In the RAS system, the angiotensin-converting enzyme 2 (ACE2) is a zinc atom-dependent metalloprotease, which catalyzes the conversion of angiotensin II to angiotensin I (Turner et al., 2002). The level of plasma ACE2 in a person is constant but varies between individuals (Hasan et al., 2020). It has been reported that SARS-CoV-2 binds to the human ACE2 via spike (S) protein C-terminal domain (CTD) (Figure 1(a)) and the SARS-CoV-2-CTD shows stronger binding affinity for human ACE2 in comparison with SARS-receptor binding domain (RBD) (Wang, Zhang, et al., 2020). The COVID-19 patients showed the symptoms of pneumonia and alveolar damage (Wang & Xu, 2020; Xu, Shi, et al., 2020). It has been shown that most of lung cells over-expressed ACE2 and the majority of ACE2 was upregulated on type II alveolar epithelial cells (AT2)(Zhao et al., 2020). It was also revealed that other types of lung cells expressed ACE2 with a limited distribution relative to AT2 (Figure 1(b)) (Zhao et al., 2020).

4. The CoV receptor distribution

The ACE2 has been suggested as an essential receptor for the SARS-CoV-2 entry (Hasan et al., 2020; Sarma et al., 2020). Extensive expression of ACE2 in various cells, such as AT2 (Zhao et al., 2020), the upper part of esophagus, epithelial cells, and absorptive enterocytes of the ileum and colon, may play a key role in multinodular SARS-CoV-2 infection. For example, Xu, Zhong, et al. (2020) explored the potential way of SARS-CoV-2 infection in different organs as well as the mucosa of oral cavity through bulk RNA-seq analysis. The outcomes revealed the presence of ACE2 in different organs as well as epithelial cells of tongue (Figure 2A(a–d)). Indeed, these outcomes have elucidated the principal mechanism that the oral cavity is basically in higher risk to SARS-CoV-2 infection and showed a piece of conformation for the ongoing inhibition approach in clinical implementation

It has been also revealed that in addition to causing fever and respiratory symptoms, COVID-19 resulted in gastrointestinal disorders including diarrhoea, vomiting and some pains in abdominal part (Gu et al., 2020). It has been indicated that SARS-CoV-2 RNA is presence in anal/rectal swabs (Xu, Li, et al., 2020; Zhang, Du, et al. 2020) and stool samples (Holshue et al., 2020; Tang et al., 2020; Young et al., 2020) of

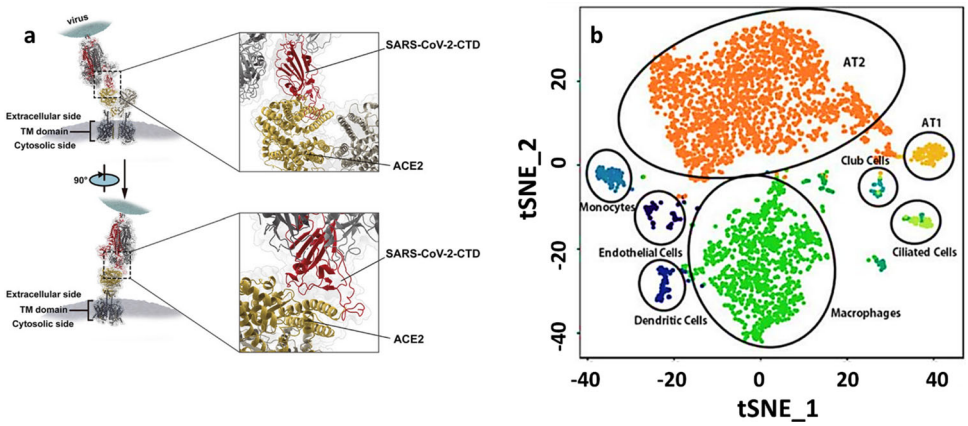

Figure 1. a The structure of human ACE2 after interaction with SARS-CoV-2 S protein (Wang, Zhang, et al., 2020). b Single-cell map of human lung cells expressing ACE-2 (Zhao et al., 2020). Reprinted with permission from Refs. (Wang, Zhang, et al., 2020; Zhao et al., 2020). Abbreviation: tSNE: t-distributed Stochastic Neighbor Embedding.

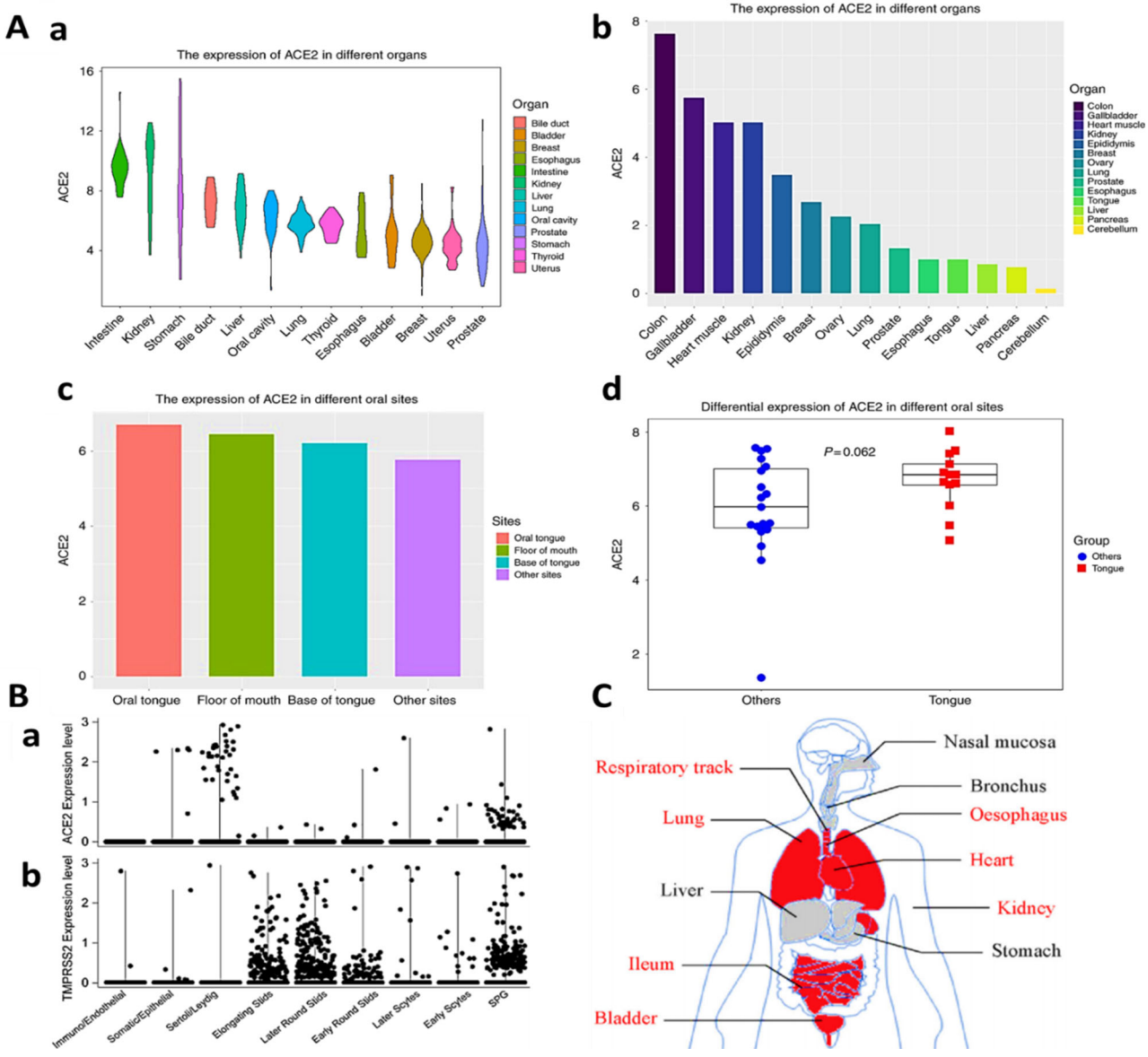

Figure 2. A: ACE2 expression pattern in different organs. a ACE2 expression from TCGA dataset. b ACE2 expression from FANTOM5 CAGE dataset. c ACE2 expression from TCGA in different oral cavity. d ACE2 expression in two kinds of oral sites and others (Xu, Zhong, et al., 2020). B: ACE2 expression pattern in human testes. a ACE2 expression in different cell types. b TMPRSS2 expression in different cells (Wang & Xu, 2020). C: SARS-CoV-2 infection-related susceptible organs, Red: high risk, Grey: low-risk (Zou et al., 2020). Reprinted with permission from Refs. (Wang & Xu, 2020; Xu, Zhong, et al., 2020; Zou et al., 2020). Abbreviations: TCGA: The Cancer Genome Atlas; FANTOM5 CAGE: Functional Annotation of The Mammalian Genome Cap Analysis of Gene Expression; SPG: spermatogonia; TMPRSS2: transmembrane serine protease 2.

patients with COVID-19 symptoms. Moreover, the viral ACE2 was revealed to be upregulated in gastrointestinal epithelial cells (Wong et al., 2020; Xiao et al., 2020).

Wang and Xu (2020) explored the sensitivity of the reproductive system to SARS-CoV-2 infection through RNA expression assay of ACE2. They found that ACE2 was remarkably upregulated in spermatogonia, Leydig, and Sertoli cells (Figure 2B(a)). Also, it has been reported recently that SARS-CoV-2 exploits the transmembrane serine protease 2 (TMPRSS2) for viral spike (S) protein cleavage (Hasan et al., 2020; Pant et al., 2020). The plots (Figure 2B(b)) indicated the pronounced upregulation of TMPRSS2 in spermatogonia and spermatids (Wang & Xu, 2020). Figure 2C also shows the SARS-CoV-2 infection-related sensitive organs which can explain about the non-respiratory symptoms identified in COVID-19 patients (Zou et al., 2020).

4.1. Lung

The distribution of ACE2 in different organs is significantly associated with the clinical symptoms of SARS-CoV-2 infection. It seems that any associated damage to the lung via external or internal factors can be mitigated by ACE2 inhibitors (Medhora et al., 2012). It has been reported that the level of pulmonary ACE2 is related to inflammatory lung disorders (Jia, 2016). Indeed, it has been well-documented that ACE2 is widley presented in the lungs (Kuba et al., 2010). It seems, the lung is the main sensitive tissue in response to SARS-CoV-2 infection (Guan et al., 2020; Wang & Xu, 2020; Yang et al., 2020).

Being involved in hemostasis, ACE2 can be considered as an important goal in the treatment of some well know diseases as well as COVID-19. However, due to the ineffectiveness of inhibitory drugs, some side effects can be observed. Some current studies are investigating the development of more potential specific ACE2 inhibitors based on chemical or biological compounds (Joshi et al., 2020). The inhibitory effects of various phases of different compounds can be investigated to reveal their concentration which inhibits the 50% of enzyme activity (Aanouz et al., 2020; Elmezayen et al., 2020). The evaluation of *Km* and *Vmax* can be used to assess the type of inhibitory mechanism by which a developed inhibitor impedes enzyme activity (Gupta et al., 2020; Muralidharan et al., 2020). The result can provide a potential model for reducing the SARS-CoV-2 infection with the ACE inhibition mechanism.

Li, He, et al. (2020) showed that the expression level of ACE2 in healthy people and patients with related disorders was not substantially different. However, relied on the increased upregulation of ACE2 in cigarette smokers, they anticipated that smoking may be identified as a risk factor for COVID-19 progression (Li, He, et al., 2020). The meta-analysis of previous results showed that ACE2 not only serves as a receptor, but it also plays an important role in post-infection mechanism such as immune system behavior, cytokine secretion, and viral viability. This result may provide a new platform for clinicians and researchers to attain more useful information regarding the pathogenesis of SARS-CoV-2 infection and to develop therapeutic platforms against COVID-19 (Li, You, et al., 2020). Pinto et al. (2020) also declared that ACE2 expression is enhanced in the lungs of COVID-19 patients with comorbidities.

4.2. Cardiovascular system

It has been well-documented that SARS-CoV-2 mainly infects alveolar epithelial cells, leading to respiratory disorders (Zheng et al., 2020). These SARS-CoV-2-induced disorders are more serious in patients with CVDs, which might be related to enhanced expression of ACE2 in these patients in comparison with healthy people. Indeed, ACE2 can be overexpressed by the consumption of some inhibitors against renin–angiotensin system (RAS) (Zheng et al., 2020). Therefore, the side effects of different therapies which might result in overexpression of ACE2 in patients infected with SARS-CoV-2 should be heedfully taken into consideration (Zheng et al., 2020).

4.2.1. Acute and chronic cardiovascular damage

Cardiac patients should be advised to take extra precautions, because the fatality rate of COVID-19 is higher in chronic CVD (Zheng et al., 2020). Patients with chronic heart disease or undergoing heart surgery have always been advised to use flu vaccines and pneumococcal vaccines at the appropriate time to prevent serious infectious and severe respiratory illness. The CoVs bind with high affinity to ACE2 receptors which are not only in the lungs, but also in other parts of the body, including the heart and digestive tract, kidney, and bladder (Hamming et al., 2004).

It has been proposed that the MERS-CoV can lead to acute myocarditis (AM) and heart-related diseases (Alhogbani, 2016). SARS-CoV-2 and MERS-CoV are similar pathogens (Elfiky & Azzam, 2020), and the AM stimulated by CoV clearly extend the adversity and complexity of patient handling. AM related to the SARS-CoV-2 can be observed in patients suffering from COVID-19, which is mostly evidenced as an enhancement in cardiac troponin I (cTnI) level (Huang et al., 2020). It was also seen that the levels of markers of AM were remarkably higher in COVID-19 patients handled in ICU, indicating that COVID-19 patients with serious stages usually show complexity involving AM (Wang, Hu, et al., 2020). Furthermore, among the identified cases of COVID-19 announced by the National Health Commission of China (NHC), a number of patients diagnosed with SARS-CoV-2 infection were primarily suffered from CVDs instead of respiratory disorders (Shi et al., 2020). Indeed, among the patients who died from SARS-CoV-2 infection with no related CVD, 12% of them suffered from considerable heart injury due to enhanced levels of cTnI (Akhmerov & Marban, 2020). Therefore, in patients with SARS-CoV-2 infection, the prevalence of AM is higher due to the systemic inflammatory behavior and immune system responses during disorder progression (Shi et al., 2020).

A follow-up survey of patients who recovered from COVID-19 revealed that around 50% suffered from CVDs

(Clerkin et al., 2020). Based on the similarity between the structures of SARS-CoV-2 and SARS-CoV, it might lead to chronic injury in the cardiovascular system, therefore serious attempts should be done to result in cardiovascular protection during handling of COVID-19 (Zheng et al., 2020).

5. Conclusion and future perspective

According to a report from China, the fatality is observed in older people as well as patients with hypertension, chronic lung disease, diabetes, and CVDs. One of the most likely mechanisms by which COVID-19 can causes lung and cardiac damage is through the SARS-CoV-2 binding to ACE2 receptors. On the other hand, diabetics, hypertensive and cardiovascular patients are the most consumers of ACE inhibitor (ACEIs) and angiotensin II receptor blockers (ARBs). ACEI drugs do not directly affect the ACE2 receptor, but inhibition of angiotensin 2 production by negative feedback increases the expression of the ACE2 mRNA. Animal studies have shown that the use of some ACE2 inhibitors as potential drugs against hypertension was associated with a several fold increase in the expression of lung and cardiac ACE2 mRNA.

There are hypotheses that some drugs trigger ACE2 overexpression and therefore enhance the severity of the COVID-19. Although the genes encoding ACE2 protein, located on the X chromosome, is more abundant in women the incidence and fatality rate of COVID-19 infection is higher in men. In addition, in spite of the decrease in the expression level of ACE2 in body, the severity and fatality rate of COVID-19 infection increases with age. The ACE2 receptor has a protective effect in acute respiratory distress syndrome (ARDS) caused by influenza. In contrast, the binding of SARS-CoV-2 S protein to the ACE2 receptor reduces the ACE2 level of lung cells and increases the associated damage. At present, with the available information, it is not possible to draw any definite conclusions about whether or not to continue taking these drugs in treating COVID-19.

Disclosure statement

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