Opinion Paper

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Role of ACE2 polymorphism in COVID-19: impact of age

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Abstract: More than 2 million people have died as a result of the COVID-19 outbreak. Angiotensin-converting enzyme 2 (ACE2) is a counter-regulatory enzyme that converts angiotensin-2 to Ang-(1–7) form in the renin-angiotensin system. Several studies have been analyzed the correlation between ACE2 and COVID-19. Indeed, ACE2/Ang (1–7) system protects the lung against acute respiratory distress syndrome by its anti-inflammatory/anti-oxidant function. However, SARS-Cov-2 can use ACE2 for host cell entry. Expression of ACE2 can be altered by several factors, including hypertension, diabetes and obesity, which also could increase the severity of COVID-19 infection. Besides, since androgens increase the expression of ACE-2, males are at higher risks of COVID-19 infection. Although reported statistics showed a significantly different infection risks of COVID-19 between adults and children, the reason behind the different responses is still unclear. This review proposes the effect of ACE polymorphism on the severity of SARS-COV-2 induced pneumonia. The previous meta-analysis regarding the effect of ACE polymorphism on the severity of pneumonia showed that polymorphism only affects the adult's illness severity and not the children. Two recent meta-analyses examined the effect of ACE polymorphism on the prevalence and mortality rate of COVID-19 and reported contradicting results. Our opinion paper suggests that the effect of ACE polymorphism on the severity of COVID-19 depends on the patients age, same as of the pneumonia.

Keywords: angiotensin-converting enzyme; COVID-19; plasma proteins; polymorphism.

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Main text

Nowadays, the world is facing the COVID 19 pandemic, which is the first pandemic after the H1N1 swine flu in 2009 and the Spanish flu in 1918. Until now (March, 2021), the virus has infected over 119 million people and taken over 2,000,000 lives. Based on the situation report-198, from January to July 2020, the highest proportion of infected people were between 25 and 64 years old. However, the age distribution pattern of the infected patients has been changed. Centers for disease control and prevention reported that in May 2020, 2.3% of the infected people were younger than nine years old, while it increased to 4% in August 2020, which is still much less than the infection rate of adult patients. The main reason behind the different infection rates between adults and children is still unclear.

Coronavirus (SARS-Cov-2) can infect and damage the lung cells, leading to acute respiratory distress syndrome (ARDS). This hyper-inflammatory state is due to a cytokine storm resulting in organ failure (e.g., lung, heart, and kidney) [1]. It has been shown that imbalance in renin-angiotensin system (RAS) is the main pathophysiological reason of ARDS. In details, RAS made up of two main arms [2]: the inflammatory axis which consists of angiotensin converting enzyme (ACE)/Angiotensin II (Ang II)/angiotensin type-1 receptor (AT1R), and the anti-inflammatory axis which includes angiotensin-converting enzyme 2 (ACE2)/Ang-(1–7)/Mas Receptor (MasR). ACE2 is a counter-regulatory enzyme that converts angiotensin-2 to Ang-(1–7) form in the renin-angiotensin system. Considering the impact of ACE2 on both arms of RAS and the opposite function of each arm, ACE2 shows a dual role in Covid-related ARDS. On the one hand, ACE2/Ang (1–7) system protects the lung against ARDS by its anti-inflammatory/anti-oxidant function through converting Ang II [3]. On the other hand, SARS-Cov-2 can use ACE2 for host cell entry. This entrance causes antiserum rise against ACE2 blocking the further virus infection [4–9]. Considering the fact that Ang II can induce its inflammatory effect through AT1R, it has been recommended to use anti AT1R drugs to control the ARDS complications [10]. Besides, higher expression of

AT1R in diabetic people, atherosclerotic sites, and hyperthyroidism may cause more intense reactions to virus [11].

ACE2 is mainly expressed in the intestines, kidneys, myocardium, vasculature and pancreas, while lower expression occurs in the respiratory system [12]. Varied symptoms and outcomes of COVID-19 might be associated with the pattern and level of human ACE2 enzyme expression in different tissues [13]. Unlike the attached type, free circulating form of ACE2 might prevent SARS-Cov-2 entry to pulmonary endothelium. Thus, the severity of COVID-19 infection can be correlated to the proportion of attached/soluble ACE2 [14].

The age-related expression of ACE2 has been shown previously. Bunyavanich et al. [15] compared the expression of ACE2 in the nasal epithelium cells, one of the first sites of COVID-19 infection, of children and adults. It has been shown that younger children have lower expressions of ACE2 compared to older children and adults. Considering the impact of ACE2 on the SARS-Covid-2 entrance, lower expressions of ACE2 may justify the less infection rates of children. Mas receptor (MasR) and ATR2, which are the anti-inflammatory components of RAS, show an age-related expression as well. Indeed, possible higher expressions of MasR and ATR2 in children can decrease the inflammatory effect of SARS-COVID-19, leading to fewer complications [16].

Some lifestyle-related factors can also affect the expression of ACE2. There is an early suggestion about the upregulation of ACE2 on the airway epithelium of smokers [17]. However, there is no consensus on how nicotine affects its expression yet [13]. Indeed, the comparison of ACE2 expression in resected lung tissue of patients with COPD, healthy lung function smokers, and healthy non-smokers showed the highest expression in COPD patients while entirely absence in nonsmoker individuals [17]. Besides, it has been shown that some chemotherapeutic agents can increase the expression of ACE2 which is beneficial for cancer treatment but can lead to higher severity of SARS-Cov-2 infection [18]. In addition, expression of ACE2 in adipocytes in response to high-fat diet makes the adipose tissue a potential target for SARS-Cov-2 virus [19].

Angiotensin overactivity can be considered the main reason for the enhanced inflammatory response of patients with hypertension, diabetes, and obesity. Indeed, considering the downregulation of ACE2 following the virus entrance, the increased rate of Angiotensin-2 leads to hyperactivity of the RAS inflammatory axis. Therefore, higher rates of mononuclear cells will be activated, which causes diffused endothelial and pulmonary inflammation [20]. However, Ragia et al. [21] recommended in their study

that different ACE2 DNA methylation patterns may cause different responses to the virus in patients with hypertension, diabetes, and obesity.

Different types of medications can also affect the expression of ACE2. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are widely used to treat cardiovascular disease. They up-regulate ACE2 expression in the heart in addition to their pharmacologic effects [22–24]. However, considering the dual role of ACE2 in the lung infection, the impact of these drugs on the ACE2 of the lungs is still unclear. Young et al. [1] reported that ACEIs/ARB therapy reduces the mortality rate of COVID-19. However, Lim et al. [25] showed the opposite results. ARBs/ACEIs are also widely used in diabetic and hypertensive patients. These drugs upregulate the Ang II and Ang I levels leading to higher expression of ACE2. Therefore, SARS-Cov-2 virus entrance to pneumocytes is facilitated. On the other hand, glycosylation caused by uncontrolled diabetes reduces ACE2 expression which makes diabetic patients more vulnerable to severe lung injuries [3].

Strong supports are behind the hypothesis that androgens are directly related to SARS-Cov-2 infection and pathogenesis. Hyperandrogenism caused by polycystic ovary syndrome (PCOS) increases asthma risk [19]. The higher prevalence of infection in men than women on the one hand and lower incidence of the disease in prepubertal children who are not exposed to androgens, on the other hand, confirm this relationship. Mini-puberty is defined as a transient expression of androgens in infants who are under one year old. It has been reported that the risk of developing severe symptoms and complications caused by COVID-19 is high in this group [14]. Shorter CAG repeat length in the androgen receptor gene on the X chromosome might be correlated with higher morbidity and mortality in COVID-19 infected men. This gene is associated with cellular activities related to prostate physiology and homeostasis [19, 26]. As reported by Wambier et al. [27], the incidence of severe symptoms in infected men with COVID-19 from younger age groups (35–45) and with no other comorbidities might be related to androgen sensitivity. In their pilot prospective observational study, 44 men admitted for severe COVID-19 in the hospital were screened and all had clinically significant androgenetic alopecia.

Consequently, anti-androgenic drugs used routinely for hair loss and benign prostate hyperplasia can be considered a candidate therapeutic for SARS-Cov-2 [27]. For instance, Spironolactone, a steroidal androgen receptor competitive blocker classified in the diuretic drugs group and provides cardio-reno protection by maintaining the

blood pressure in the normal range, might be a potential candidate for SARS-Cov-2 treatment in the early stages of the infection [14].

Considering the impact of ACE on ACE2 expression, our hypothesis suggests that ACE polymorphism may have a role in different reactions to COVID-19 infection. Studies showed that the majority of the ACE gene polymorphism (47%) is related to insertion/deletion (I/D) polymorphism, which is associated to the absence or presence of 287-bp sequence in 16 intron of ACE gene on chromosome 17q23 [28]. Since this polymorphism is located in a non-coding region, this cannot be considered a functional variant. However, the I/D polymorphism can affect both plasma and tissue levels of ACE [29]. This variety leads to different ACE activity between DD, II and DI genotypes. Those with DD genotype had the highest and those with II genotype had the lowest ACE activity [30]. The correlation between I/D polymorphism and cardiovascular disease, blood pressure, atherosclerosis, muscle performance, diabetic nephropathy Alzheimer and pneumonia have been shown previously [28].

Studies showed conflicting results regarding the effect of ACE polymorphism on the risk of pneumonia. A meta-analysis reported a significant effect of polymorphism on the risk of pneumonia among adults but not among children [31]. Another study was done on the correlation between ACE polymorphism and pediatric pneumonia. It was shown that there was not significant difference between pneumonia patients and controls regarding various ACE polymorphism genotypes [32]. Besides, Garde et al. [33] showed in their study that in the Dutch white adult patients, ACE2 polymorphism had no significant effect on the severity of pneumonia. Thus, the influence of ACE2 polymorphism

on the severity of pneumonia differs based on the age and ethnicity of the patients (Figure 1).

In the case of the Coronavirus, Delanghi et al. [34] showed that ACE I/D polymorphism affects the distribution and pathogenesis of COVID-19 while other ACE polymorphisms (complement C3 [F and S alleles], HFE [C282Y mutation], haptoglobin [Hp1 and Hp2 alleles] and vitamin D binding protein [DBP1 and DBP 2 alleles]) had no significant effect on the pervasiveness of COVID-19. In details, they analyzed the correlation between each polymorphism and COVID-19 by comparing the prevalence of each allele and the rate of COVID-19 mortality in each region. Results revealed a negative correlation between D allele and the prevalence and mortality of COVID-19 [34]. However, Saadat [35] questioned their outcome by mentioning the higher rates of both COVID-19 patients and D allele holders in Eastern Asia compared to Europe. Also, Hatami et al. [36] performed a meta-analysis regarding the correlation between I/D ACE polymorphism and showed that the presence of I or D allele has no significant effect on the mortality of COVID-19. These controversies can be justified by considering that reported COVID-19 prevalence is a multifactorial phenomenon that depends on the socioeconomic condition and the hereditary factors as well as age [35]. Both of the aforementioned analyses did not consider the age of their samples. Thus, subgroup analyses based on the age of the patients might solve the conflicts as it did for pneumonia. Based on this hypothesis, performing cross-sectional or cohort studies to compare the prevalence of I/D polymorphism among mild and severely affected patients might partly explain the morbidity and mortality of COVID-19 in healthy patients.

Figure 1: Age-dependent effect of ACE I/D polymorphism on the severity of pneumonia.

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