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Sex-dependent immune response and lethality of COVID-19

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ABSTRACT

COVID-19 has spread to all countries around the world after it was first discovered in Wuhan of China at the end of 2019. It is caused by a novel coronavirus called SARS-CoV-2 with much semblance to SARS-CoV including the sequence homology and disease symptoms. It is reported to be more infectious than SARS-CoV due to higher binding affinities between its spike protein and the ACE2 receptor on cell surface. Despite this, its case fatality rate is much lower compared with that of SARS-CoV although it varies in different countries. However, the case fatality rate increases steadily with age and it is reported to be the highest in aged COVID-19 male patients in almost all countries. Consistent with these, females have higher antiviral immune responses. Males and females are different in inflammatory response and aberrantly hyperactive cytokines are the main lethal causes of COVID-19. Interestingly, the gene encoding the ACE2 receptor protein and some genes encoding the immune regulatory proteins such as TLR7 are located on X chromosome which is subject to X chromosome inactivation and sex hormone regulation. These may account for some sex-dependent immune responses and lethality observed in COVID-19 patients. In general, children are less likely to be infected with SARS-CoV-2 and only less than 1% of pediatric COVID-19 patients may die of COVID-19. However, the most severe pediatric cases become multisystem inflammatory syndrome that is similar to Kawasiki disease with features of viral infection. Since most infected kids were boys in China, there may be sex-dependent immune response in pediatric COVID-19 cases as well.

1. Introduction

In late 2019 a severe acute respiratory syndrome (SARS)-like pneumonia was first reported in Wuhan of China (Li et al., 2020a; Zhu et al., 2020). At the early 2020, the virus that causes this disease was isolated and its viral sequence was identified in Wuhan Institute of Virology (Zhou et al., 2020). This novel virus bears the hallmark of coronaviruses with an envelope containing spike proteins. It is a positive single-strand RNA virus with a genome size of approximately 30 kilobases which are the largest among all RNA viruses. It shares about 80% sequence homology to the SARS-CoV virus which causes SARS and 50% sequence identities to another closely related coronavirus MERS-CoV which causes Middle East respiratory syndrome (MERS) (de Wit et al., 2016; Zhang and Holmes, 2020; Zhou et al., 2020). Since it also causes pneumonia resembling SARS, it was named SARS-CoV-2 by World Health Organization (WHO) and its associated disease after infection was named COVID-19. There are many good reviews regarding the structure, infection and symptoms of this RNA virus already. Therefore, we will not discuss them much in this review. Instead, we will focus on the fatalities of COVID-19 that may be dependent on sex and age. We will try to uncover why females and children may be less susceptible to COVID-19.

As of Dec. 12, 2020, more than 70 million people have been infected with SARS-CoV-2 worldwide based on the official tallies by all nations. The fatality rate of COVID-19 is relatively low compared with SARS or MERS and it varies among different ethnic groups in different countries around the world. It is reported to be close to 2.2% for the whole world with over 70 million cases. The case fatality rate is about 1.9% in the US with over 16 million reported cases and it is around 2.6% in Brazil with close to 7 million confirmed cases. It is 2.4% in France and 1.6% in Germany with over 2.4 million and 1.3 million reported cases, respectively. It is around 1.4% in Japan with about 175,000 cases and only 0.8% in Israel with over 350,000 confirmed cases. It is even lower in Singapore with just 0.05% fatality rate out of 58,000 confirmed cases. But it is over 3.5% in a few countries such as Italy and Great Britain with each over 1.8 million reported cases. And it even reaches 9% in Mexico with over 1.2 million cases. In China where the virus was first detected,

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it is close to 5.0% with almost 95,000 reported cases. However, the case fatality rate has been dropping to almost zero now after China has adopted a nationwide early detection and early treatment emergency healthcare system. This indicates that early intervention is critical for prevention of high case fatality rates of COVID-19.

Like SARS, sepsis is the most common lethal complication which was present in nearly all fatal COVID-19 cases (Imai et al., 2005; Nowill and de Campos-Lima, 2020). Other common complications of SARS and COVID-19 are respiratory failure and acute respiratory distress syndrome (ARDS) that may be lethal (Mangalmurti and Hunter, 2020). Aberrant interferon activity and inflammatory response are often observed in the severe COVID-19 cases (Hadjadj et al., 2020). The case fatality rate is also dependent on other factors besides cultural and ethnic differences of the countries around the world (Casanova et al., 2020). Interestingly, there is already enough evidence indicating that old male patients form the most susceptible group of the human populations to COVID-19, which is the focus of this review.

2. General features of COVID-19

2.1. Symptoms of COVID-19 patients

COVID-19 patients display a broad spectrum of symptoms. Fever, cough and shortness of breath are most common symptoms shared by a majority of patients (around 70% or above) (Docherty et al., 2020; Li et al., 2020b). Fatigue, vomiting and diarrhea are also common among these patients (Docherty et al., 2020; Li et al., 2020b). Some may have headache, chest discomfort and muscle pain. A minor portion of COVID-19 patients do not exhibit much symptoms who are called asymptomic patients (Docherty et al., 2020). Most symptoms appear to result from the problems in the respiratory and enteric systems.

2.2. Risk factors for COVID-19

There are a number of factors that may influence the outcome of COVID-19 patients. It appears that old male patients are more susceptible to SARS-CoV-2 and have a higher chance to become the fatal victim of COVID-19 (Akbar and Gilroy, 2020; de Lusignan et al., 2020; Docherty et al., 2020; Li et al., 2020b; Mallapaty, 2020a; Williamson et al., 2020). The immune system in the aged patients may be more likely to become overly inflammatory (Akbar and Gilroy, 2020). There are other co-morbidity risk factors for mortalities in COVID-19 such as the pre-existing conditions for the patients with cardiovascular disease, hypertension, diabetes, pulmonary disease, kidney disease, dementia, asthma, obesity, etc. (Docherty et al., 2020; Schultze et al., 2020). Some ethnic groups may have higher chance of being infected with the virus, but it may be related to social and economic conditions of these ethnic groups since they may not be able to practice adequate social distancing to prevent viral infections. Smoking could be another risk factor although there are some conflicting results (de Lusignan et al., 2020; Williamson et al., 2020).

2.3. Expression, processing and function of ACE2 receptor

SARS-CoV-2 uses ACE2 as the receptor for viral entry into the cells (Figs. 1 and 2), similar to what SARS-CoV did during the previous SARS

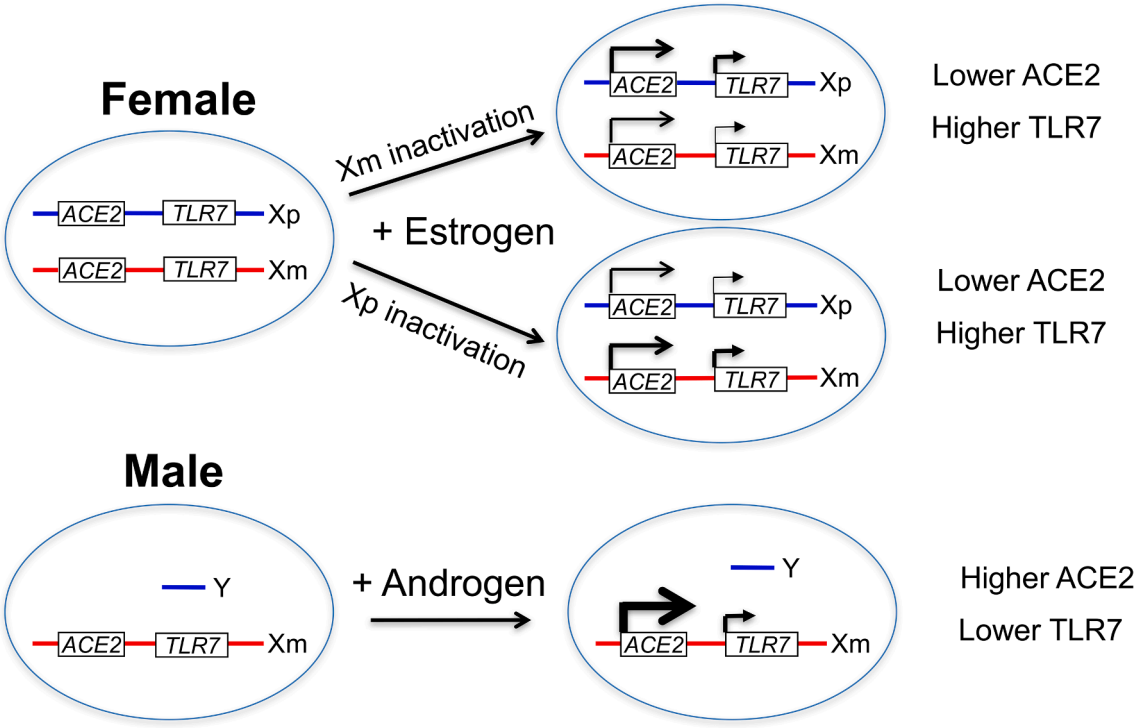

Fig. 1. Regulation of *ACE2* and *TLR7* gene expression on X chromosome. Both *ACE2* and some immune regulatory genes such as *TLR7* are located on X chromosome. The ACE2 gene was reported to largely escape X chromosome inactivation in most tissues in females. Thus, the *ACE2* gene is expressed at relatively high level (more than half) from its allele located on the randomly inactivated paternal X (Xp) or maternal X (Xm) chromosome, compared with its counterpart on the active X chromosome. The *ACE2* gene is only expressed from the active maternal X (Xm) chromosome in the males since it is not present on Y chromosome. Expression of the *ACE2* gene is also regulated by estrogen in the females and androgen in the males. It may be regulated by other sex hormones too. As a result of sexual hormone regulation, the ACE2 protein is present at higher levels in most cells in the males compared with the females. Thus, expression of *ACE2* is dependent on sex hormones whereas its expression level may not be regulated by X inactivation in females. By contrast, the *TLR7* gene is subject to random X chromosome inactivation in females so that it is only expressed at much lower level (much less than half) from its allele located on the randomly inactivated X chromosome, compared with the other allele on the active X chromosome. However, its expression may not be regulated by sex hormones. Therefore, it has higher expression level in the females due to extra expression of the *TLR7* gene from the inactivated X chromosome, compared with the males.

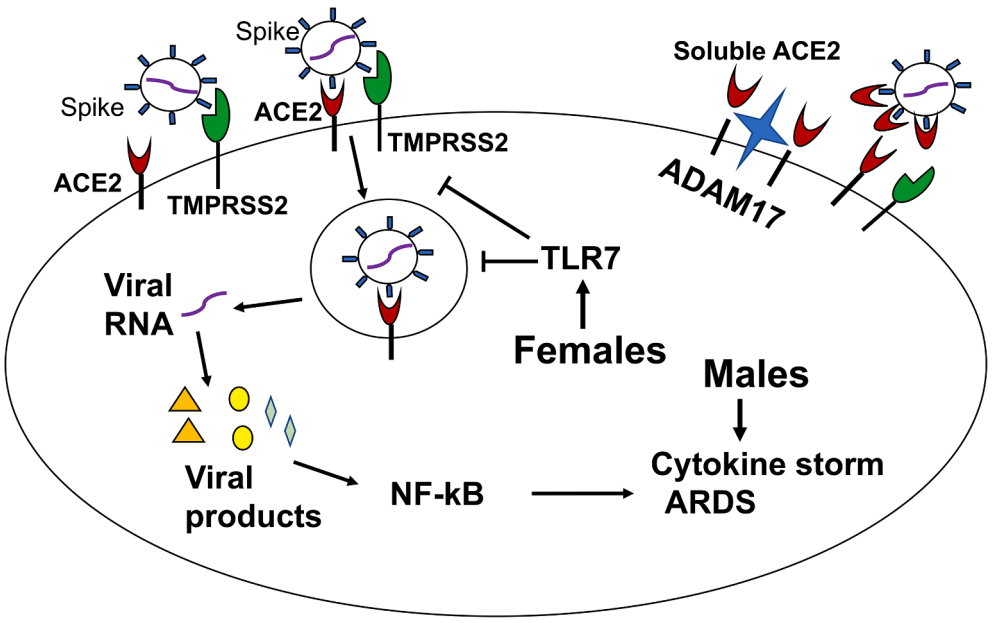

Fig. 2. Sexually dimorphic regulation of COVID-19 immune response. SARS-CoV-2 uses ACE2 as the receptor for infection. The spike protein on the envelope of the coronavirus SARS-CoV-2 is first activated after being processed by the transmembrane protease TMPRSS2 before it can bind to the ACE2 receptor attached to the cell membrane. Then the attached virus undergoes endocytosis and the viral RNA is released into the cytoplasm afterwards. After being amplified by RNA-dependent RNA polymerase (RdRP), the viral RNA transcripts are processed and then viral products are generated. These will induce NF-kB and other immune regulatory factors which will cause cytokine storm and ARDS in the infected COVID-19 patients. Male hormones will enhance these immune responses. By contrast, females have higher TLR7 and other immune regulatory proteins which result in higher antiviral response by prevention of binding of the virus to the receptors on the cells or inhibition of uncoating of virus inside the cells. The membrane-bound ACE2 receptor can be cleaved by ADAM17 to become soluble ACE2 which can inhibit the binding of spike proteins on the envelope of the virus to the ACE2 receptor on the cell membrane.

outbreak (Li et al., 2003; Wang et al., 2020; Zhou et al., 2020). ACE2 were reported to be essential for infection by SARS-CoV or SARS-CoV-2 (Gargaglioni and Marques, 2020; Hoffmann et al., 2020; Zhou et al., 2020). The *ACE2* gene is located on the X chromosome (Fig. 1) (Gemmati et al., 2020; Gheblawi et al., 2020). Interestingly, it is reported that the human *ACE2* gene may escape X inactivation in 80% of females with the *ACE2* allele on the inactive X chromosome expressing about half amount of the transcript expressed from the *ACE2* allele on the active X chromosome, and yet it displays male-biased expression in most tissues (Fig. 1) (Tukiainen et al., 2017). This male-biased *ACE2* transcription may be because its transcription is regulated by different sex steroid hormones present in the males versus females which is different from regulation mediated by X chromosome inactivation (Fig. 1) (Liu et al., 2010; Tukiainen et al., 2017). Its sexual dimorphic human *ACE2* gene expression varies in different tissues and organs, with lung and liver as two of the organs with notable male-biased *ACE2* transcript levels (Bunders and Altfeld, 2020; Pirola and Sookoian, 2020; Tukiainen et al., 2017).

ACE2 is expressed in human airway epithelial cells which are susceptible to COVID-19 infection (Ziegler et al., 2020). It is also expressed in the liver and gastrointestinal tract, with particularly high levels of expression observed in the small intestine and ileum (Gargaglioni and Marques, 2020; Pirola and Sookoian, 2020). ACE2 is also highly expressed in the testis, kidney, heart, thyroid and adipose tissues. Moderate to low levels of ACE2 expression have also been observed in the bladder, adrenal gland, brain, muscle, spleen, blood and blood vessels (Gargaglioni and Marques, 2020). It is worth noting that ACE2 is present in testis but not in ovary, which might be one of the reasons why males are more susceptible to SARS-CoV-2 (Liu et al., 2020).

The ectodomain of ACE2 is cleaved by ADAM17 and it is shed before SARS-CoV-2 can infect the cells (Fig. 2) (Gheblawi et al., 2020). It is reported that there is membrane-bound and soluble ACE2. The membrane-bound ACE2 is required for the viral entry, whereas the soluble ACE2 is a risk factor for COVID-19 (Sward et al., 2020). Human soluble ACE2 was able to block the entry of SARS-CoV-2 in human blood vessel and kidney organoids (Monteil et al., 2020). Age and sex may influence the levels of soluble ACE2 (Sward et al., 2020). Therefore, this may be another reason for sex-biased infection of SARS-CoV-2.

ACE2 is thought to normally protect the mouse lung from ARDS and edema in an *Ace2* knockout mouse (Imai et al., 2005). Loss of ACE2 may result in higher vascular permeability in the lung and increased production of inflammatory cytokines (e.g. IL6 and IFNγ) and chemokines (Gheblawi et al., 2020; Imai et al., 2005). ACE2 is an important player in the RAS (renin-angiotensin system) pathway which will be discussed in more detail below (Ziegler et al., 2020). ACE2 deficiency also stimulates more shedding of ACE2 by ADAM17 and causes over-activation of RAS. On the other hand, ACE2 depletion caused by SARS-CoV-2 infection may tip the balance between ACE1 and ACE2 to be in favor of inflammatory and vasoconstrictive responses regulated by ACE1/angiotensin II axis.

2.4. *RAS (renin-angiotensin system) pathway*

ACE2 is the enzyme for conversion of angiotensin I (Ang-I) into Ang 1–9 which is cleaved by ACE1 to generate Ang 1–7 (Gheblawi et al., 2020). ACE2 can also directly convert angiotensin II (Ang-II) into Ang 1–7. Ang 1–7 binds to Mas receptor (MasR) which protects cardiovascular system. ACE1 and ACE2 are counteracting and their balance is important for the RAS (renin-angiotensin system) pathway which regulates blood pressure, vasodilation or vasoconstriction (Gemmati et al., 2020; Gheblawi et al., 2020). RAS is also required for regulation of capillary permeability and volume control. It is involved in inflammatory response, coagulation, fibrosis, etc.

2.5. *TMPRSS2 expression*

TMPRSS2 is required to prime S protein before COVID-19 can bind to this ACE2 receptor (Fig. 2) (Gheblawi et al., 2020; Hoffmann et al., 2020). ACE2 is also cleaved by TMPRSS2 at the sites different from the ones targeted by ADAM17-mediated shedding (Xiao et al., 2020). TMPRSS2-cleaved ACE2 undergoes shedding which is also required for viral entry of SARS-CoV-2 into the cells. The *TMPRSS2* gene is an androgen-responsive gene (Gemmati et al., 2020; Wambier and Goren, 2020). Estrogen can also increase its expression. However, estrogen level falls in the females after menopause (Gemmati et al., 2020). This

may be another reason why old males are prone to SARS-CoV-2 infection.

3. Sex-specific effects of COVID-19

3.1. Men are more prone to COVID-19 with higher mortalities

There are many studies already demonstrating that male patients may be more susceptible to COVID-19 and exhibit higher fatality rates compared with the female patients with similar ages and ethnic social backgrounds (Docherty et al., 2020; Gadi et al., 2020; Lu et al., 2020; Williamson et al., 2020; Zhang et al., 2020). Higher androgen levels and related phenotypes appear to be correlated with increased viral load and transmission in the patients (Wambier and Goren, 2020). There are more men infected with COVID-19 in some countries, but it is opposite in other countries with more women COVID-19 patients (Gargaglioni and Marques, 2020). Nevertheless, male patients tend to display more severe symptoms and higher mortalities although these also vary among different countries (Griffith et al., 2020; Scully et al., 2020; Sharma et al., 2020). The highest ratios of male/female mortalities caused by COVID-19 have been reported in Dominican Republic, Netherlands, Greece and Romania, with a ratio of around 2 or above (Gargaglioni and Marques, 2020; Scully et al., 2020; Sharma et al., 2020). Although sex-related genetic differences between males and females may predispose the males to COVID-19, it can also result from the sex-dependent differences in some preexisting adverse health conditions and social behavior that make the males to be at disadvantage in prevention of the viral infection (Griffith et al., 2020; Sharma et al., 2020). It was reported that male pediatric patients accounted for a majority of the infected children in China (Lu et al., 2020).

3.2. Sex-dependent differences in related coronaviruses

It is also reported that more male patients died from severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS) that were caused by two other related coronaviruses (Mauvais-Jarvis et al., 2020; Scully et al., 2020; Sharma et al., 2020). SARS-CoV also uses ACE2 as the receptor for viral infections, whereas MERS-CoV binds to DDP4 before it enters the cells (Li et al., 2003; Raj et al., 2013). These suggest that there may be similar mechanisms underlying the human disease susceptibilities to coronaviruses since these three coronaviruses use two different receptors for viral infections and yet there are higher mortalities among the male patients infected by all three viruses. A plausible explanation is that there may be sex-dependent host responses upon viral infections.

3.3. Sex-dependent differences in mouse models

Mouse models have been generated to investigate the infection and pathogenic mechanisms of the SARS-CoV, MERS-CoV and SARS-CoV-2 (Bao et al., 2020; Dinnon et al., 2020; Gu et al., 2020; Jiang et al., 2020; Li and McCray, 2020; Roberts et al., 2007; Sun et al., 2020a, 2020b). Similar sex and age effects had been observed in the mice upon the viral infection (Dinnon et al., 2020; Gargaglioni and Marques, 2020). Young adult mice were resistant to viral infection and aged mice developed more severe diseases reminiscent of human patients (Dinnon et al., 2020; Frieman et al., 2012). Male mice were more severely affected with much higher death rates compared with the female mice (Channappanavar et al., 2017). Sex hormones had been reported to have different effects on the mice infected with SARS-CoV. Estrogen could stimulate immune response and protect against SARS, whereas testosterone and progesterone were found to have the opposite effects (Fig. 2) (Bunders and Altfeld, 2020; Gargaglioni and Marques, 2020).

3.4. Sex-biased immune responses of COVID-19 patients

Excessive immune response is common among COVID-19 patients. It may lead to cytokine storm and septic shock which may result in death of the affected patients (Nowill and de Campos-Lima, 2020). There are sex-specific immune responses based on previous studies (Klein and Flanagan, 2016). Females are more susceptible to autoimmune diseases than males. The viral load in the blood is lower in the females compared with the males. Males and females also respond differently to vaccines (Aaby et al., 2020; Bunders and Altfeld, 2020; Hampton, 2020). These differences are caused either by expression of X-linked genes or by different sex hormones present in the males and females (Klein and Flanagan, 2016). About 60 genes in the immune response are located on the X chromosome that may be expressed at different levels in the females compared with the males because there are two copies of X-linked genes in the females but only one copy of them present in the males (Fig. 1) (Mauvais-Jarvis et al., 2020; Scully et al., 2020). Most genes on the X chromosome are subject to X chromosome inactivation so that the gene dosage may be compensated in the males versus the females. About 15–25% of X-linked genes may fully or partially escape X chromosome inactivation and display variable sex-biased expression in different tissues (Tukiainen et al., 2017). Thus, differential expression of some important X-linked genes in the immune system may make females and males respond differently to COVID-19. For example, the X-linked *TLR7* gene activates expression of type I interferons such as IFNα and IFNβ (Fig. 1) (Vikse et al., 2020). However, COVID-19 inhibits production of type I interferons which negatively regulates viral infection. Therefore, sex-biased expression of TLR7 and its effect on TLR7-mediated type I interferon production may be partly responsible for the differences in the anti-viral responses observed in the male and female COVID-19 patients (Fig. 2).

Furthermore, sex hormones have been shown to be important regulators in the immune system (Gargaglioni and Marques, 2020; Klein and Flanagan, 2016). This may also contribute to sexual dimorphism in the immune responses observed in COVID-19 patients (Bunders and Altfeld, 2020). Estrogen stimulates immune response, whereas testosterone and progesterone may inhibit it (Fig. 2) (Bunders and Altfeld, 2020; Gargaglioni and Marques, 2020). Estrogen binds to estrogen receptors which activate transcription of many cellular target genes including those in the immune cells. Estrogen may suppress the transcription of inflammatory cytokines and chemokines which may result in cytokine storm that can kill the COVID-19 patients. By contrast, testosterone and progesterone may counteract the effects of estrogen. Targeting these steroid hormones may be beneficial for future therapies against COVID-19 with anti-inflammatory effects.

In general, both innate and adaptive immune responses are stronger in females than males (Gadi et al., 2020; Hampton, 2020; Klein and Flanagan, 2016). Indeed, it is reported that female patients tended to have much stronger as well as more sustainable T cell responses upon COVID-19 infection than male patients in a study carried out by the researchers of Yale University in the US (Takahashi et al., 2020). Male patients were shown to have significantly fewer T cells. The cytokines IL-8 and IL-18 in the innate immune response were significantly higher in male patients compared with the female patients in one cohort study (Takahashi et al., 2020). Many other cytokines and chemokines were present in the patients of both sexes at much higher levels compared with the normal people (Takahashi et al., 2020).

4. Pediatric patients with COVID-19

4.1. SARS-CoV-2 infection in children

In general, kids are less likely to be infected with SARS-CoV-2. It is rare for the infected kids to be hospitalized and less than 1% of pediatric cases may become fatal (Pierce et al., 2020; Snape and Viner, 2020; Swann et al., 2020). It may not be because of the reduced ACE2 levels in

the respiratory tract of the kids as one might have suspected (Ortiz et al., 2020). Nevertheless, more and more children have been infected with SARS-CoV-2 worldwide as the pandemic continues. They may spread the virus to other people who are more vulnerable even though most pediatric patients only had mild or no symptoms (Dong et al., 2020; Lu et al., 2020; Mallapaty, 2020b; Sinha et al., 2020). Therefore, we need to pay more attention to the COVID-19 cases in children so that these SARS-CoV-2 transmissions can be detected in time and isolated accordingly before spreading to vulnerable populations in the society.

Infected kids with comorbidities such as preexisting heart problems were more likely to be admitted into the hospitals and may need intensive care. Often they had fever and may also have nausea, vomiting, diarrhea and shortness of breath with increasing ages of the affected children which are typically found in adult COVID-19 patients (Swann et al., 2020). Interestingly, a majority of the infected children in China were reported to be males (Lu et al., 2020). Due to school closure during the pandemic, the long-term effect for the kids may be felt years later with social, psychological and educational consequences.

4.2. *Kawasaki-like disease*

A small portion of the infected children did show more typical COVID-19 symptoms including ARDS (Sinha et al., 2020). Some severely affected pediatric patients may develop hyper-inflammatory Kawasaki-like disease or multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) which is commonly associated with viral infection (Christakis, 2020; Couzin-Frankel, 2020; Mallapaty, 2020b; Pierce et al., 2020; Snape and Viner, 2020; Swann et al., 2020). These infected kids with Kawasaki-like disease often have fever and rash that may be caused by the overactive immune system with cytokine storm. There is a chance of gastrointestinal symptoms such as vomiting and diarrhea for the pediatric patients. They may even suffer heart, shock and blood pressure problems which can be fatal even though death is rare among the infected children (Couzin-Frankel, 2020). About half of PIMS-TS kids in the UK and US develop myocarditis and have transient myocardial dysfunction (Snape and Viner, 2020). They are substantially older than traditional Kawasaki patients, with high levels of inflammatory marker ferritin and two cardiovascular damage makers (D-dimer and troponin) in the circulating blood which has not been observed previously in the Kawasaki pediatric patients (Snape and Viner, 2020). The long-term medical consequences for the PIMS-TS children are presently unknown and their health condition may need to be checked again later.

5. Conclusion

COVID-19 has been wreaking a havoc around the world since it was first detected about a year ago. SARS-CoV-2 is much more infectious than SARS-CoV although it has much lower case fatality rate. Many of the infected people do not show any obvious symptoms. This makes the mass detection a necessity today so that all virus carriers can be quarantined and spread of the virus will be curtailed in the human populations. Infection rate in children is much lower than that of adults. However, they can pass the virus to susceptible people without notice. Old male COVID-19 patients are most vulnerable, in particular those with comorbidities such as diabetes and heart diseases. The antiviral immune system and the inflammatory response seem to be sex-dependent. A large of portion of the lethal COVID-19 cases are caused by hyperinflammatory responses termed cytokine storm. Therefore, it may be helpful to treat male and female patients differently by taking into account of sex-dependent immune system and then apply some sexually different regimen to these patients so that there will be most suitable antiviral immune response afterwards. This may reduce the case fatality rate of COVID-19 and help to make it a more manageable disease, together with vaccine and other useful strategies. The world economy and the well-being of humans will benefit greatly from less infectious SARS-CoV-2 and less lethal COVID-19.

Declaration of Competing Interest

The authors 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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