Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-Associated Urogenital Disease: A Current Update

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Severe Acute Respiratory Syndrome Coronavirus 2, which is quickly spreading around the world and causes coronavirus disease 2019, may attack the urogenital system. We thought that a summary of the current literature about urogenital disease associated with the virus would be useful for physicians treating patients with coronavirus disease 2019. PubMed was comprehensively screened for studies published from 2019 to 2020. Studies of coronavirus disease 2019 patients with kidney disease, reproductive system diseases, or urological cancer were included. Through reviewing current literature, we summarized that acute kidney injury is a risk factor for patients with coronavirus disease 2019 and is related to their survival. A diagnosis of chronic kidney disease increases the risk of infection. The therapy for kidney transplant patients should be cautious and implemented on a case-by-case basis. When the public health burden is too heavy to bear, a rational selection of treatment for patients with urological cancer is vital. The male reproductive system is at high risk of being attacked by the virus, which may cause damage to reproductive function, and the long-term effects require further study. So, the complications associated with the urogenital system should not be ignored during the course of infection treatment and more robust evidence of long-term effects on the urogenital system will be proposed as more studies are published.

Keywords: Humans; Infections; Reproductive health; Severe acute respiratory syndrome coronavirus 2; Urogenital system

INTRODUCTION

Coronaviruses, one member of the Coronaviridae family, are common pathogens infecting humans and other mammals. An infection with one of these viruses usually causes a self-limited cold or some mild symptoms in the gastrointestinal tract and upper respiratory tract [1]. However, coronavirus of the severe acute respiratory syndrome (SARS-CoV) and coronavirus of the Middle East respiratory syndrome (MERS-CoV) are two exceptions, they caused two outbreaks in the last few decades with a relatively high mortality rate, and more than 10,000 people were infected [2].

Beginning in December 2019, some patients with symptoms similar to viral pneumonia were identified in Wuhan, Hubei Province, China. The outbreak spread rapidly from Wuhan to almost all regions of China and subsequently throughout the world. Using
a high-throughput sequencing analysis, a novel coronavirus that is closely related to a SARS-like coronavirus from bat [2] was identified and named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the Coronaviridae Study Group [3]. The infection caused by this virus was called coronavirus disease 2019 (COVID-19), which was declared a pandemic by the World Health Organization on March 11, 2020. Up to October 5, 2020, this virus has infected 34,804,348 people and caused the death of 1,030,738 patients around the world (https://covid19.who.int/), and the number continues to increase.

In addition to the usual symptoms in the lungs, complications of urogenital system and damage to the reproductive system have frequently been reported, which have attracted the attention of urologists. Thus, we performed a comprehensive search for studies examining urogenital diseases associated with SARS-CoV-2 to improve our understanding and guide clinical treatment.

ANGIOTENSIN-CONVERTING ENZYME II

1. Mechanisms of invasion through angiotensin-converting enzyme II

Angiotensin-converting enzyme II (ACE2), a type I integral membrane glycoprotein, is an essential negative regulator of the renin-angiotensin system that generates angiotensin II to balance the functions of ACE and exerts a significant protective effect on the cardiovascular system and other tissues [4]. SARS-CoV-2 invades ACE2-expressing cells with the assistance of ACE2 and does not take advantage of receptors of other coronaviruses [5], indicating that ACE2 may play a vital role in mediating SARS-CoV infection [6]. Recent studies inferred the potential mechanism of SARS-CoV-2 binding to ACE2 through the viral S protein. The S1 subunit facilitates the interaction between the virus and ACE2, and then the S2 fusion peptide inserts into the membrane to complete the endocytosis of the ACE2-SARS-CoV-2 complex [4]. The cellular serine protease Tmprss2 plays a crucial role in the acid-dependent proteolytic cleavage of the S protein, and the endosomal cysteine proteases cathepsins B and L (CatB/L) also participate in S protein priming [7].

2. Distribution of angiotensin-converting enzyme II in urogenital organs

ACE2 is expressed at a relatively high level in the kidney. All proximal tubule cells show higher expression of ACE2 than other cell types, 5% to 15% of both straight and convoluted proximal tubule cells overexpress ACE2 [7], and relatively high coexpression has also been detected in podocytes and proximal straight tubule cells [8]. According to the public bladder single-cell datasets, ACE2 is expressed at low levels in all epithelial cell types and shows a decreasing trend from the outer layer to the inner layer of the bladder epithelium [9].

Meanwhile, a recent study observed ACE2-expressing cells in almost all testis and Sertoli cells, accounting for the largest proportion of all ACE2-expressing cells and suggesting that the testis may be the target organ of SARS-CoV-2 and somatic cells in the testis, particularly Sertoli cells, may be more susceptible to SARS-CoV-2 infection than germ cells [7].

The prostate has been highlighted as a potential organ that is sensitive to SARS-CoV-2 infection, as Song et al [10] detected prostate epithelial cells that coexpressed Tmprss2 and ACE2, with a higher proportion in club and hillock cells. Additionally, we analyzed the distribution of ACE2 in organs of the urinary system based on data from The Genotype-Tissue Expression database and The Cancer Genome Atlas, and summarized the specific localization pattern of ACE2 reported in previous studies, as shown in Fig. 1 for comparison.

EFFECT OF COVID-19 ON THE KIDNEY

1. SARS-CoV-2-associated acute kidney injury

A multicenter study from New York reported that the incidence of acute kidney injury (AKI) was 36.6% (1,993/5,449) in 5,449 patients with COVID-19. Among people with AKI, 14.3% of patients (285/1,993) required renal replacement therapy and the mortality rate was 35% (694/1,993). Moreover, a close relationship between AKI and respiratory failure has been reported, as 89.7% of patients (1,068/1,190) who required mechanical ventilation developed AKI compared with 21.7% of patients (925/4,259) without mechanical ventilation [11]. Additionally, a retrospective study including 701 patients with COVID-19 treated at Wuhan Tongji Hospital reported a relatively high prevalence of renal dis-
ease in patients upon admission (rate of albuminuria: 43.9%, and rate of hematuria: 26.7%) and approximately 5.1% of patients developed AKI during hospitalization, which exerted a significant effect on the in-hospital death rate (p<0.001) [12].

AKI often coexists with fatal manifestations, such as respiratory failure, and is associated with mortality during hospitalization, leading to a poor prognosis. Therefore, we should be more alert to AKI and monitoring is indispensable, particularly for patients with abnormal renal function at the time of admission. Moreover, the occurrence of AKI and respiratory failure may coexist; thus, when people show one symptom we should prevent the other disease. However, the incidence of AKI varies significantly among different countries or regions. Therefore, we summarized recent research analyzing AKI in patients with COVID-19 to improve people’s understanding and facilitate follow-up analyses with a quick reference (Table 1) [11-24].

Currently, the main mechanism of AKI in patients with COVID-19 is being widely discussed. First, electron microscopy of renal tissues obtained after an autopsy of 26 patients who died of COVID-19 showed significant clusters of coronavirus particles in tubular epithelial cells and podocytes, indicating that the virus is able to directly attack the kidney. Significant acute tubule injury was detected using light microscopy, mainly due to red blood cell obstruction of the microvascular lumen, resulting in endothelial injury and changes in glomeruli and blood vessels, which potentially leads to hematuria, proteinuria, or AKI [25]. Second, the early response to SARS-CoV-2 infection leads to the overproduction of pro-inflammatory cytokines, namely, cytokine storms, which increase vascular permeability and cause abnormal coagulation function, leading to multi-organ functional injury [26]. Finally, systemic hypoxia caused by lung damage and nephrotoxicity related to large quantities of drugs used for therapy may be meaningful factors that contribute to AKI and should not be ignored.

2. SARS-CoV-2-associated chronic kidney disease

Chronic kidney disease (CKD) covers a wide range of patients with different clinical symptoms. At the early stage, patients may not present any obvious symptoms, but almost all functions of kidney are eventually lost [27]. A study of COVID-19 in Washington State showed

![Diagram of organ distribution of angiotensin-converting enzyme II (ACE2) in human organs.](https://xenabrowser.net/datapages/)
that 86% of patients (18/21) had complications, of which CKD was the most significant (48%, 10/21) [13], and CKD might increase the possibility of a poor prognosis for patients with COVID-19 [28]. Additionally, another study reported that many patients with CKD or hypertension consistently use angiotensin receptor blockers and ACE inhibitors, which would upregulate the ACE2 receptor, increasing the risk of SARS-CoV-2 infection [29]. However, controversy exists regarding whether these patients should change drugs to decrease the infection risk. Thus, the conditions of patients with CKD must be monitored, people with CKD should be protected prior to infection, and the most suitable drug should be determined.

3. Kidney transplantation in patients with COVID-19

Recently, most studies have mainly focused on patients with COVID-19 who have normal immune function. However, reports of the immunosuppressed population are rare; these people may have different responses to or clinical features of COVID-19 because their immune responses, particularly the T cell immune responses, have been significantly suppressed by immunosuppressants [30]. Kidney transplant patients are representative of this population. A summary of 10 patients with COVID-19 who had undergone a kidney transplant showed that these transplant recipients had more severe symptoms (five severe and three critical patients vs. nine mild and one severe patients, p<0.01), a longer course of the disease (35.3±8.3 days vs. 18.8±10.5 days, p<0.01) and a longer virus shedding time (28.4±9.3 days vs. 12.2±4.6 days, p<0.01) than the control group. These results confirmed the greater risks for immunosuppressed population during this pandemic [31]. However, immunosuppression might decrease the risk of cytokine storms, and thus the optimal balanced therapies for patients with COVID-19 who are kidney transplant recipients remain controversial and an objective evaluation of the effects of immunosuppression on these patients is necessary. According to the most recent report, researchers recommend that kidney transplant recipients remain controversial and an objective evaluation of the effects of immunosuppression on these patients is necessary. According to the most recent report, researchers recommend that kidney transplant recipients remain controversial and an objective evaluation of the effects of immunosuppression on these patients is necessary.

Table 1. A summary review of recent COVID-19 related studies about AKI

| Journal                | Author                  | Total (n) | Age (y)*          | Male (n) | Female (n) | AKI† | Non-survivor† |
|------------------------|-------------------------|-----------|-------------------|----------|------------|------|--------------|
| Kidney Int             | Hirsch et al [11]       | 5,449     | 64 (52–75)        | 3,317    | 2,132      | 1,993 (36.58) | 694 (12.74) |
| Kidney Int             | Cheng et al [12]        | 701       | 63 (50–71)        | 367      | 334        | 36 (5.14)    | 113 (16.12)  |
| JAMA                   | Arentz et al [13]       | 21        | 70 (43–92)        | 11       | 10         | 4 (19.05)    | 11 (52.38)   |
| BMJ                    | Chen et al [14]         | 274       | 62 (44–70)        | 171      | 103        | 29 (10.58)   | 113 (41.24)  |
| N Engl J Med           | Guan et al [15]         | 1,099     | 47 (35–58)        | 640      | 459        | 6 (0.55)     | 15 (1.36)    |
| Lancet                 | Huang et al [16]        | 41        | 41 (41–58)        | 30       | 11         | 3 (7.32)     | 6 (14.63)    |
| J Clin Med             | Lim et al [17]          | 160       | Non-AKI: 67 (24–92) | 86       | 74         | 30 (18.75)   | 44 (27.50)   |
| J Am Soc Nephrol       | Pei et al [18]          | 333       | 56.36±13.4        | 182      | 151        | 35 (10.51)   | 29 (8.71)    |
| JAMA                   | Richardson et al [19]   | 5,700     | 63 (52–75)        | 3,437    | 2,263      | 523 (9.18)   | 553 (9.70)   |
| Intensive Care Med     | Ruan et al [20]         | 150       | Died: 67 (15–81)  | 102      | 48         | 23 (15.33)   | 68 (45.33)   |
|                        |                         |           | Discharged: 50 (44–81) |         |            |          |              |
| Intensive Care Med     | Tu et al [21]           | 174       | Non-survivors: 70 (64–80) | 79       | 95         | 19 (10.92)   | 25 (14.37)   |
|                        |                         |           | Survivors: 51 (37–62) |          |            |          |              |
| JAMA                   | Wang et al [22]         | 138       | 56 (42–68)        | 75       | 63         | 5 (3.62)     | 6 (4.35)     |
| Lancet Respir Med      | Yang et al [23]         | 52        | 59.7±13.3         | 35       | 17         | 15 (28.85)   | 32 (61.54)   |
| Lancet                 | Zhou et al [24]         | 191       | 56 (46–67)        | 119      | 72         | 28 (14.66)   | 54 (28.27)   |

The incidence of AKI and mortality rates of COVID-19 listed in the table were obtained by dividing the number of patients with the target event by the total number of patients. Recent COVID-19 related studies about AKI were summarized and the number, age and sex of patients in each study, as well as the percentage of patients with AKI and the percentage of deaths were counted. This will be conducive to a comprehensive understanding of SARS-CoV-2-associated AKI.

COVID-19: coronavirus disease 2019, AKI: acute kidney injury, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

*Values are presented as median (interquartile range) unless otherwise specified. †Values are presented as mean±standard deviation according to references. ‡Values are presented as number (%).
of COVID-19 should be admitted to the intensive care unit (ICU), undergo mechanical ventilation, the immunosuppressive drugs, such as CNIs or antiproliferative drugs, should be discontinued immediately and glucocorticoid doses may increase [32]. All of these studies have provided valuable clinical experience for us and the idiographic treatment plan should be determined flexibly according to the specific conditions of patients. The renal function of these patients must be monitored.

EFFECT OF SARS-COV-2 ON THE REPRODUCTIVE SYSTEM

1. SARS-CoV-2-associated impairments in gonadal function

The study by Ma et al [33] examined 100 age-matched healthy men and 81 male patients with COVID-19. The serum luteinizing hormone (LH) and serum prolactin levels were significantly increased in male patients with COVID-19 (p<0.0001) and the ratios of testosterone to LH levels and follicle-stimulating hormone to LH levels were obviously decreased (p<0.0001), indicating that this virus may alter gonadal function to subsequently affect male fertility. Additionally, the risk of orchitis caused by SARS-CoV-2 should not be overlooked, as Bian [34] performed autopsies of patients who died due to COVID-19, including 37 systematic autopsies and 54 minimally invasive autopsies, and observed reduced numbers of and damage to spermatogenic cells, as well as viral particles and RNA of SARS-CoV-2 in the testes. These findings provide direct evidence of SARS-CoV-2-induced damage to the testes and a self-evident subsequent reduction in testicular function. Moreover, severe sepsis due to infection might further evolve into disseminated intravascular coagulation (DIC) [35]. The testicle is an organ with a large microvasculature and has a high potential risk of infection. Therefore, the risk of thromboembolism in testis caused by DIC in the testicle must not be ignored. Furthermore, DIC may promote the formation of microthrombi, which narrow the microvessels of the penile tissue and inhibit blood circulation, further affecting the function of nerves, such as erection-related nerves, and potentially causing the patient to experience symptoms of erectile dysfunction or aggravate the original manifestations; similar results have been reported in patients with cancer who are receiving anti-cancer therapies [36].

2. SARS-CoV-2-associated sexual transmission

Testicular immune privilege normally protects the immunogenic germ cells from the host response. However, certain viruses are able to cross the blood-testis barrier, enter cells of the male reproductive tract, and elicit an immune response within the testicle [37]. Researchers have not yet determined whether SARS-CoV-2 uses the testis as a viral reservoir or spreads through sexual behaviors. One study examined the level of the SARS-CoV-2 RNA in semen samples from 12 convalescent patients and testicular samples from a patient who died of COVID-19 in the acute phase, but SARS-CoV-2 was not detected in the semen of patients in the recovery phase or the testis of patients who died during the acute phase [38]. Another study including 34 Chinese adult male patients did not detect the virus in the semen at 31 days (interquartile range: 29–36 days) after the diagnosis of COVID-19, but 18% of patients (6/34) presented with scrotal discomfort due to viral inflammation before and after the diagnosis of coronavirus [39]. Interestingly, in a recent study by Li et al [40], the virus was detected in 15.8% of patients (6/38) with COVID-19, including 26.7% (4/15) in the acute phase, and 8.7% (2/23) in the recovery phase. All of the studies described above are limited by small sample sizes and some objective conditions. However, under the severe conditions of the pandemic, these studies have provided valuable information about clinical experiences. Meanwhile, the contradictory results obtained by these studies highlights our limited knowledge of the effects of SARS-CoV-2 on the reproductive system, which deserves further study.

Scholars have proposed some hypotheses about the mechanisms by which SARS-CoV-2 invades the testis. Pan et al [39] proposed that a load of virus associated with the severity of symptoms may be an important factor allowing the virus to cross the blood-testis barrier, and studies exploring alternative biological mechanisms by which SARS-CoV-2 alters the testicular microenvironment are necessary. Liu et al [7] observed high expression of the cysteine proteases CatB/L and CD147, which are closely associated with the invasion of this virus, in many different cells in the testis.

Although evidence proving that SARS-CoV-2 propagates through semen is insufficient, we should not un-
derestimate the risk of infection through sexual transmission. Researchers have proposed that many sexual behaviors, such as oral-anal contact, might lead to the spread of the virus because SARS-CoV-2 has been detected in saliva and feces, ACE2 was also detected in the mucosa of the oral cavity and glandular cells of the rectal epithelia [41].

3. Effects of potential treatments for COVID-19 on the reproductive system

Remdesivir (development code GS-5734), which is considered a promising drug for the treatment of COVID-19, is a new nucleoside analog that competitively binds and inhibits the RNA-dependent RNA polymerase of a variety of coronaviruses, thereby further inhibiting viral replication [42].

However, nucleoside analogs potentially exert deleterious effect on gonadal function, gametogenesis, and embryo development, which may cause fetal malformation [43]. Relatively high levels of residual GS-5734 have been detected in the testes and epididymis during the early stage of administration [42]. Thus, drug toxicity to the reproductive system has attracted the attention of scholars, but clinical studies in this area still rare; therefore, the long-term effects of GS-5734 on the reproductive system require further study and this drug should be used with caution.

Several clinical studies have shown that the infection-related mortality rate in women is lower than that in men, and women achieve better clinical results. A study from Tongji Hospital in Wuhan showed better clinical outcomes for women than men that were strongly correlated with women’s early warning status and female hormone levels, particularly estrogen (E2) levels [44]. E2 exerts a protective effect on SARS-CoV-2 infection by inhibiting the production of inflammatory factors and regulating the host immune response [45], which also leads to the emergence of one potential treatment for patients with COVID-19 by administering female hormones. However, female hormones affect the male reproductive function, and if exogenous estrogen is administered as a drug into the body, it will undoubtedly disrupt the normal hormone balance, the normal sexual desire, erectile function, or sperm production.

SARS-CoV-2 infection rates in patients with prostate cancer treated with androgen deprivation therapy (ADT) are significantly lower than in patients with prostate cancer who are not treated with ADT [46]. The potential mechanism is that ADT reduces the expression of TMPRSS2, a key protein required for the virus to attack the prostate. Meanwhile, the decrease in androgen levels reduces the production of immune factors in the body and alleviates the cytokine storm [46]. Based on these findings, some evidence supports the hypothesis that ADT may be a treatment for COVID-19. However, the feasibility of this method of treatment should be very carefully evaluated. ADT leads to androgen deficiency that may cause the penile dorsal nerve and cavernous nerve to become deprived of hormonal nourishment and undergo degenerative changes; at the same time, the trabecular smooth muscle structure and the structure and function of vascular endothelium in the penis will also change, increasing the probability of venous leakage [47]. Furthermore, changes in hormone levels and the neurological status may further lead to multiple reproductive dysfunctions, such as erectile dysfunction and decreased libido, and researchers have not yet determined whether the damage can be reversed over time.

4. Perspectives of SARS-CoV-2-associated changes in the reproductive system

Differences in hormone levels between men and women may be one of the important explanations for the differences in the clinical presentation and prognosis of COVID-19 between men and women [44]. The high expression of ACE2 and TMPRSS2 genes in the testis and prostate may also put men at a disadvantage in terms of the invasion of SARS-CoV-2, which may partially explain the higher infection rate and poorer prognosis in men than in women [7,10]. Potential treatments based on those genes should be carefully evaluated with due consideration of the effects on the reproductive system and should be used judiciously. As our understanding of COVID-19 improves, asymptomatic infected persons are attracting increased attention. However, sufficient clinical research supporting the presence of the virus in the semen of asymptomatic infected persons and its potential for sexual transmission is lacking. Therefore, further research on these patients is still needed. At the same time, considering the potential of SARS-CoV-2 to invade the testicular tissue and the risk of spread, we also suggest that contraceptive measures, such as condoms or avoiding sexual behaviors, are necessary during the period of
SARS-CoV-2 infection. Furthermore, the convalescent male should closely monitor his reproductive function to avoid long-term virus-induced damage to the reproductive system.

**EFFECT OF COVID-19 ON UROLOGICAL CANCERS**

The situation for patients with cancer has become difficult during the COVID-19 pandemic. A multicenter study involving 105 patients with cancer diagnosed with COVID-19 and 536 age-matched patients without cancer who were diagnosed with the coronavirus showed that a SARS-CoV-2 infection concomitant with cancer was associated with a higher observed mortality rate in patients with cancer (odds ratio [OR], 2.34; 95% confidence interval [CI], 1.15–4.77; p=0.03), a higher ICU admission rate (OR, 2.84; 95% CI, 1.59–5.08; p<0.01), a greater incidence of at least one severe OR critical symptom (OR, 2.79; 95% CI, 1.74–4.41; p<0.01), a faster rate of deterioration and a longer duration of hospitalization than in noncancer patients (p<0.01) [48]. A retrospective study of 28 patients with cancer selected from 1,276 patients with COVID-19 reported similar conclusions: 53.6% of patients (15/28) developed a severe clinical condition, 35.7% of patients (10/28) experienced life-threatening complications, such as adult respiratory distress syndrome (ARDS), sepsis and acute myocardial infarction, and the death rate was 28.6% (8/28) [49].

The majority of patients with COVID-19 are elderly and often have a poor prognosis [14,22,23]. Additionally, the incidence of various tumors in the urinary system, such as bladder cancer and prostate cancer, is also higher in the elderly population. Therefore, the population of patients with urinary cancer is worthy of attention. Immunotherapy and other relevant anticancer therapies should be used with caution in patients with advanced or aggressive tumors to prevent the death of normal human cells, such as lung epithelial cells, due to the release of large amounts of cytokines [48]. At the same time, excessive production of cytokines may aggravate the cytokine storm caused by a viral infection, increase the severity of ARDS, and increase the mortality rate of patients. Thus, the management of therapies administered to patients with cancer to prevent infection with the virus is necessary. A group of experts from Europe and the United States discussed the triage of urological surgeries during the period of the COVID-19 pandemic and recently presented a priority list of urological surgeries that considered the aggressiveness of the disease, the effects of short-term delays in care and the possibility of alternative treatments [50]. Experts recommend nonsurgical treatments should be considered whenever possible for common urological conditions, when medical resources are scarce, operations should be carried out according to the list of operations reported in the article [50]. Subsequently, a multicenter study from Italy correlated this strategy with real data from hospitals to assess the real effects of these recommendations on urological practice. The study included 2,387 major urological cancer surgeries performed at three centers, of which 32.3% were classified as a high priority surgery according to the recommendations [51]. This study not only revealed the importance of rational surgical object selection in the context of the COVID-19 pandemic but also proved that when the availability of health care resources is reduced, approximately two-thirds of elective major urological surgeries for tumors can be safely delayed or treated using an alternative method.

**CONCLUSIONS**

SARS-CoV-2 is still widespread worldwide, and its threat to the urogenital system should not be ignored. Therefore, we reviewed the most recent literature to improve our understanding of these diseases. AKI often leads to a poor prognosis for patients with COVID-19, and the direct attacks on the kidney and indirect effects of cytokine storms are important causes. Patients with CKD and kidney transplant patients are at a high risk of infection due to decreased immunity or body functions, and thus the renal function of these people must be monitored. In particular, the appropriate adjustment of immunosuppressive agents should be closely monitored in the immunosuppressed population. SARS-CoV-2 infection may lead to impairments in male reproductive function, and the long-term effects deserve further study. Meanwhile, researchers are still debating whether the virus is capable of sexual transmission at different times. The effect of potential treatments on the reproductive system should be considered before their implementation. Moreover, urologists must rationally select surgical patients with urological carcinomas when medical resource shortages exist. Mean-
while, with further exploration of SARS-CoV-2, the mechanism and therapy for urogenital diseases related to this virus may also be elucidated in the near future, and we will closely monitor these topics in the future.

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**Conflict of Interest**

The authors have nothing to disclose.

**Author Contribution**

Conceptualization: GC, WJ. Data curation: GC, WJ. Formal analysis: FX, MZ. Supervision: HN. Validation: FX, MZ. Visualization: GC, WJ. Writing – original draft: GC, WJ. Writing – review & editing: GC, WJ, HN.

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