Review Article

Lower Urinary Tract Symptoms (LUTS) Related to COVID-19: Review Article

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The pandemic of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) or Coronavirus Disease 2019 (COVID-19) is still ongoing. The outbreak of this new emerging contagious disease has impacted a wide range of sectors including health and economics. Much information about COVID-19 has been discovered by many laboratories, and action taken in various ways as quickly as possible to inhibit the outbreak. It was found that COVID-19 is a ribonucleic acid virus (RNA virus) that can cause infection among humans. Moreover, it can mutate and spread contagiously mainly through the respiratory system. The most common symptoms are cough and fever. Many patients could develop to either pneumonitis or respiratory failure. The SARS-CoV-2 virus can infect various organs, the main infections being in lungs and rectum. In these cases, many laboratories can isolate the virus from oropharyngeal and nasopharyngeal swab and then apply the reverse transcription polymerase chain reaction (RT-PCR) test to identify the COVID-19 virus. Many of the viral infections can cause cystitis by immunologic response. There is a study that showed the SARS-CoV-2 virus could be isolated from the urine sample. The patients had significant changes in urinary storage for frequency, urgency, and urinary incontinence during infected period, which improved after the disease resolved. Moreover, there is a study that reported that the COVID-19 patients who had the International Prostate Symptom Score (IPSS) scores of 20 to 35 had significantly longer hospital stays, more frequent intensive care requirements, and higher mortality rates. Therefore, physician and medical personnel should be aware of the irritative voiding symptoms that might be the presenting symptoms of COVID-19. Furthermore, as many studies have shown that the virus can be excreted in urine, thus, the virus could be contagious via urinary contamination.

Keywords: COVID-19, LUTS, Lower urinary tract symptoms, Viral cystitis

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The pandemic of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) or Coronavirus Disease 2019 (COVID-19) was discovered in Wuhan, China in December 2019, and spread throughout the world. The outbreak of this new emerging contagious disease has impacted a wide range of sectors including health and economy. To date, there have been more than a hundred million cases throughout the world and more than two million people have died from this disease [data from the World Health Organization (WHO), dated 16/2/2021][1]. In Thailand, more than twenty thousand patients have suffered from COVID-19 and eighty people have died (data from the Department of Disease Control of Thailand on 16/2/2021)[2]. Much information about COVID-19 have been reported by many laboratories, and action taken in various ways as quickly as possible to inhibit the outbreak. It was found that COVID-19 is a ribonucleic acid virus (RNA virus) that caused infection among humans. Moreover, it can mutate and spread contagiously mainly through the respiratory system. The most common symptoms are cough and fever. Many patients could possibly develop to either pneumonitis or respiratory failure, especially in elderly and patients with co-morbid diseases, which might develop into critically ill and eventually dead. The SARS-CoV-2 virus can infect various organs, the main infections being in lungs and rectum. In these cases, many laboratories can isolate the virus from oropharyngeal and nasopharyngeal swab and then apply the reverse transcription polymerase chain reaction (RT-PCR) test to identify the COVID-19 virus[3,4]. The viral infection can be transmitted by aerosol and feces, and many physicians and scientists have also suspected that the virus might be shed into urine.

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Viral cystitis

Regarding to the previous studies, many of the

viral infections can cause cystitis by immunologic response. Many studies have shown that Polyomavirus hominis1 (BK virus) can present in urine and plasma of patients who have had immunosuppressant conditions. After their immune systems were reconstituted, an immune response to the virus resulted in inflammation of the bladder mucosa and caused bleeding with storage voiding symptoms from cystitis[5,6]. One study involved a case report of cystitis resulting from Influenza B viruses in a thirty-one-year-old man. He had dysuria, urinary frequency, and hematuria while he was infected. His symptoms resolved after recovering[7]. Moreover, Adenovirus, which typically causes mild respiratory tract infection, can also cause hemorrhagic cystitis, but this was a rare manifestation[8].

COVID-19 and LUTS

A study showed that the SARS-CoV-2 virus could be isolated from the urine sample in a seventy-two-year-old man on the twelfth day after the infection. This was first described in Guangzhou, China in February 2020. Therefore, it is possible that the SARS-CoV-2 virus could be contagious and transmitted to other people by urine[9].

Symptoms, diagnosis, and management

The study by Mumm et al reported an increase in urinary frequency in seven out of 57 patients who tested positive for SARS-CoV-2. These patients had, on the average, voided 13.5 micturitions per day. All patients were excluded from urinary tract infection, acute renal injury, or prostatitis. Interestingly, this group of patients had cough and fever, numbering only 5 and 3, respectively. One patient presented as the urosepsis, and none of the urinalysis and urine culture demonstrated any sign of infection. None of the urine specimens tested positive SARS-CoV-2 by RT-PCR[10].

Kaya et al from Turkey have described that the lower urinary tract symptoms (LUTS) might be one of the early presenting symptoms of COVID-19 patients. They found no significant change in voiding symptoms in both male and female patients. On the other hand, the patients had significant changes in storage symptoms for frequency, urgency, and urinary incontinence while infected. The storage symptoms improved after the disease resolved. The authors mentioned that the cause of storage symptoms would have been from viral cystitis, which was similar to other viral infections. However, hydration therapy while they were infected might be the cause of frequency urination, and psychogenic LUTS from depressive condition[11]. All patients were treated as conservative therapy, there were no specific treatment.

Furthermore, two meta-analysis studies reported the detection rate of SARS-CoV-2 virus in urine sample of the COVID-19 patients. Kashi et al reported that the detection rate was about 4.5%, and the viral shedding frequency was 1.18%, which was lower than in the rectum and the nasopharyngeal. The detection rate of viral shedding into urine is higher in patients who have moderate and severe disease and could be detected from day one to day fifty-two after the onset of the disease[12]. Another study reported the detection rate was 8%, compared to 21.3% from blood and 39.5% from stool. Moreover, the detection of virus in the urine was associated with greater severity of the disease and higher mortality[13].

Prognosis

Several studies mentioned the prognosis of COVID-19 patients who had lower urinary tract symptoms or other related urological conditions. Liu et al had found the amount of red blood cell in urine and proteinuria were significantly higher in the COVID-19 patients than in the healthy group. The patients who had glucosuria or proteinuria were more likely to have severe or critical conditions[14]. Additionally, there is a study reporting that the COVID-19 patients who had the International Prostate Symptom Score (IPSS) scores 20 to 35 had significantly longer hospital stays, more frequent intensive care requirements, and higher mortality rates[15].

Pathophysiology

To date, it is unclear for the pathophysiology of the SARS-CoV-2 virus infection causing the lower urinary tract symptoms. Some studies stated that the lower urinary tract symptoms might be due to the replication of these RNA viruses in the urothelial cells or inflammation from the immunological response. There are recent studies reporting the SARS-CoV-2 transmitted to cells via angiotensin converting enzyme 2 (ACE-2) receptor, which is present in lungs, kidney, esophagus, bladder, ileum, heart, and endothelial cells[16]. ACE-2 receptor could be found in the proportion of 2.4% in the bladder urothelial cell. Thus, the bladder would be at high risk of infection in viremia stage and result in viral cystitis[17]. Furthermore, the SARS-CoV-2 virus can cause endothelitis in several organs, which could irritate the bladder and lead to irritative voiding symptoms, as many studies show negative result

in urinary PCR. Meanwhile, the study reported by Lamb et al revealed the expression of interleukin (IL)-6, IL-1β, C-reactive protein, and tumor necrosis factor (TNF)-α in serum of COVID-19 patients. IL-6 was found to be the best prognostic indicator of COVID-19 severity. Moreover, they found the level of inflammatory cytokines IL-6, IL-8, and IP-10 are significantly increased in urine of COVID-19 patients. All patients in this group reported de novo urinary urgency, increased urinary frequency, and nocturia[18].

The correlation between androgen and COVID-19 severity of LUTS

Many studies have been reported that the incidence of COVID-19 infections has been higher in male than in female patients, with male patients being at a greater risk of the infection developing into severe disease and more serious complications, especially in elderly men[19]. Moreover, studies have shown that prostate cancer patients treated with androgen deprivation therapy (ADT) were found to have fourfold to fivefold less severe symptoms than non-ADT group. There is evidence that the gender disparities resulted from the role of sex hormonal effect, particularly androgen[20,21]. Several studies found that androgen can increase the expression of ACE-2 receptor and Transmembrane protease serine type 2 (TMPRSS2) resulted in facilitate viral entry into the host cells[22]. Being similar to the ACE-2 receptor, the TMPRSS2 is expressed in lungs, heart, kidneys, livers, colon, esophagus, brain, gall bladder, testis, and prostate glands[23]. Moreover, the androgen can modulate immune response by increasing neutrophil function and various cytokines[24]. These factors could explain the male patients are more susceptible to the disease severity and progression than the female, including LUTS. Furthermore, Samuel et al also found that benign prostatic hypertrophy (BPH) patients were associated with COVID-19 hospitalization[25]. However, the data about androgen effect related to LUTS severity in COVID-19 patients remain limited and needs for further studies.

Discussion

Due to the severe pandemic of COVID-19, the healthcare systems have been encountering problems of shortage of blood in the blood bank, medical equipment, and healthcare workers. The healthcare systems policy relating to reduce the unnecessary hospital visit of the patients has been introduced to preserve the medical resources and reduce the risk of COVID-19 exposure. Therefore, the authors suggested that the medical personnel should balance between the delaying of the diagnosis and treatment, the patient's safety, and the available medical resources. Alternatively, for patients who have a mild degree of lower urinary tract symptoms (LUTS) without signs of complications such as hematuria, urinary tract infection, or urinary retention, the authors suggest that the diagnosis and treatment might be based on the telemedicine. In addition, the European Association of Urology (EAU) has proposed the guidelines and recommendations about urology care during this situation. The guidelines recommend that the surgical procedure for non-high risk prostate cancer, low grade bladder cancer, less than T2 renal mass and stage I seminoma patients can be postponed. The obstructed or infected kidneys should be diverted and decompressed; on the other hand, the non-obstructing stones operations should be delayed[26]. Even though many studies have shown that the virus might be contagious via urine contaminate, there is no recommendation to do urine RT-PCR before performing urologic procedures. Therefore, the healthcare workers who must perform the procedures that expose them to the urine should use proper personal protective equipment as a universal precaution. The study by Raza et al recommends using face shields or high-resistance fluid penetration face visors, goggles, performing appropriate donning and doffing of the shoes cover and gowns, and using fluid-resistant (Type IIR) surgical masks for non-aerosol generating procedures[27].

Can et al reported that elderly patients (over 50-years-old) have more severe LUTS than younger group[28]. Therefore, an increased LUTS may be the presenting symptoms of COVID-19 in elderly patients. These might provide the evidence to support the proactive screening in elderly patients who have increased LUTS in those areas that have outbreak of COVID-19.

Conclusion

Although the pathophysiology of COVID-19 associated cystitis is still unclear, which could be from directly infected bladder tissue or consequence of immunological responses, many studies have shown that the SARS-CoV-2 virus infection can cause irritative voiding symptoms. Therefore, physician and medical personnel should be aware that irritative voiding symptoms might be the presenting symptoms of COVID-19. Furthermore, as many studies have shown that the virus can be excreted in urine, the virus could be contagious via urinary contamination.

What is already known on this topic?

The COVID-19 is an RNA virus causing infection among humans. Moreover, it can mutate and can spread contagiously mainly through the respiratory system. The most common symptoms are cough and fever. Many patients could possibly have developed to pneumonitis or respiratory failure. Additionally, the SARS-CoV-2 virus can infect various organs, the main infections being in lungs and rectum. Many laboratories can isolate the virus from oropharyngeal and nasopharyngeal swab and then apply the RT-PCR test to identify the COVID-19 virus.

What this study adds?

The SARS-CoV-2 virus could be isolated from the urine sample tested by the RT-PCR. The SARS-CoV-2 virus infection can cause irritative voiding symptoms and patients who have more severe urinary irritative voiding symptoms have significantly longer hospital stays, more frequent intensive care requirements, and higher mortality rates. Moreover, many studies have shown that the virus can be excreted in urine, thus, the virus could be contagious via urinary contamination.

Conflicts of interest

The authors declare no conflict of interest.

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