The Prevalence and Risk Factors of Storage Urinary Symptoms in Symptomatic COVID-19 Patients Who were Treated in Cohort Ward and Field Hospital

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ABSTRACT

Objective: The primary aim of this study was to focus on the prevalence of storage symptoms in COVID-19 patients and the factors associated with those symptoms.

Material and Methods: We collected the data of COVID-19 patients who were admitted to the cohort ward, ICU and field hospital of Thammasat University Hospital, Thailand, between May and June 2021. Patients answered online survey questions and undertook urinalysis by urine dipstick test. The online survey questions related to symptoms of COVID-19 infection, number of daytime voiding, nocturia, frequency and urgency symptom during COVID-19 infection, OABSS and ICIQ-LUTS in the part of storage symptoms subscale.

Result: There were 136 COVID-19 patients who met with the eligible criteria and were willing to participate in the study. Patients who had storage symptoms totaled 61 (44.85%) and had average daytime frequency, nocturia and proportion of urgency higher than no storage symptom group (5.9 VS 3.8, 2.0 VS 1.0 and 67.21% VS 6.67% (p-value <0.001), respectively). The OABSS and ICIQ storage subscale in the storage symptoms group were higher than normal group, 3.2 VS 0.9 and 4.5 VS 1.7 (p-value < 0.001), respectively.

Conclusion: Our study demonstrated that the SARS-CoV-2 virus infection is associated with abnormal storage symptoms which include frequency, urgency and nocturia. The storage symptoms may be associated with the severity of COVID-19 disease.

Keywords: Storage symptoms; COVID-19; SARS-CoV-2 virus; viral cystitis (Siriraj Med J 2022; 74: 134-141)

INTRODUCTION

Since the pandemic of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) or Coronavirus Disease 2019 (COVID-19) has spread around the world in 2019, the outbreak is still ongoing with no end in sight. The main infected organ is the respiratory tract[1,2]; however, the SARS-CoV-2 virus can also infect the urinary tract, especially the bladder. Previous studies have reported that SARS-CoV-2 virus could be isolated from a urine sample.[3] Patients who were infected had a high prevalence of abnormal urinary storage symptoms; urinary frequency, urgency and urinary incontinence.[4,5] Moreover, the severity of urinary storage symptoms and the presence of hematuria and proteinuria from urinalysis is related to the severity of COVID-19 disease and mortality rate.[6] In Thailand, the high rate of outbreak occurred during the second, third and fourth wave. The second wave was caused by the SARS-CoV-2 strain GH,

the third wave by the SARS-CoV-2 strain B1.1.7 (alpha strain) and the fourth wave by the SARS-CoV-2 strain B.1.617 (delta strain). The intensive care requirement and the mortality rate of the third and fourth waves were significantly higher than those of the second wave. The primary aim of this study was to focus on the prevalence of storage symptoms in COVID-19 patients and the factors associated with those symptoms. Another aim of our study was to study the abnormal urinalysis related to the severity of COVID-19 infection.

MATERIAL AND METHODS

This study was cross-sectional. We collected the data of COVID-19 patients, aged between 18 to 60 years old, who were admitted to the cohort ward, ICU and field hospital of Thammasat University Hospital, Pathumthani, Thailand, between May and June 2021. Inclusion was restricted to COVID-19 patients who could use smartphones to respond to our online survey questions. Patients who had clinical presentation of suspicious bacterial cystitis (had dysuria or urine dipstick test positive for nitrite or leukocyte esterase), patients who were foreigners, patients who had unstable medical conditions or indwelling urethral catheter, were excluded.

We reviewed the hospital records relating to collected data about age, gender, body mass index (BMI), underlying diseases, symptoms and complications of the COVID-19 infection. Patients were informed and consented to this study by telephone. Patients who met with the eligible criteria and were willing to participate in the study answered the online survey questions by themselves and undertook urinalysis by urine dipstick test at wards. The online survey questions consisted of symptoms of COVID-19 infection, number of daytime voiding, number of nocturia, whether they voided more frequently during COVID-19 infection, whether they had urgency symptom during COVID-19 infection, whether they had increased number of nocturia during COVID-19 infection, or whether they had urgency incontinence during COVID-19 infection. OABSS (Overactive Bladder Symptoms Scores) questionnaire (total score 15) and ICIQ-LUTS (International Consultation on Incontinence Modular Questionnaires - Lower Urinary Tract Symptoms) in the part of storage symptoms subscale (total score 16).

Patients who had any one of the following, which were cough, runny nose, sore throat and nasal congestion were defined as having upper respiratory tract infection symptoms (URI). Patients who had any one of the following, which were URI symptoms, fever, anosmia, chest discomfort, rash, diarrhea, pneumonia were defined as being in the symptomatic COVID-19 infection group. Patients who

did not develop any symptoms were defined as being in the asymptomatic COVID-19 infection group. Pneumonia was diagnosed by chest x-ray that was reported by a radiologist.

The OABSS is the questionnaire that contains questions including all the important content of storage symptoms, which are frequency >7 times, urgency, nocturia and urge incontinence. Therefore, storage symptoms group was defined by using the criteria that patients had to answer that they developed one or more symptoms of frequency, urgency, nocturia, urge incontinence concomitant with having OABSS equal to or greater than 1 score during infection. Patients who did not develop any storage symptoms during infection or had OABSS score 0 were defined as no storage symptoms group.

Patients who had BMI equal to or greater than 25 kg/m² were defined as obesity group in this study.

The urine dipstick test that showed any of the following; those which were leukocyte positive, proteinuria or hematuria were classified as a positive result.

The data were analyzed by using STATA statistical software version 15.0. We used the student T-test for parametric data, Mann-Whitney U test for non-parametric data and Fisher-Exact test for categorical data. The binary regression analysis was used for analyzing factors that were associated with storage symptoms in COVID-19 infection patients. The statistically significant were defined as p-value <0.05.

RESULTS

From 2,357 COVID-19 patients admitted, there were 136 (5.77%) COVID-19 patients who met the eligible criteria and were willing to participate in the study; 61 (44.85%) patients had storage symptoms and 75 (55.15%) patients did not have storage symptoms.

For the demographic data as shown in Table 1, patients were divided into two groups by answering the question as to whether they had storage symptoms concomitant with OABSS score ≥1 during the COVID-19 infection, which was defined as having storage symptoms and patients who not develop any storage symptoms or had OABSS score 0 were defined as no storage symptoms. The mean age of COVID-19 patients who had storage symptoms was 36 years old and 33 years old for patients who did not have storage symptoms, which were not statistically difference between the groups. There were 37 (60.66%) patients in the storage symptoms group who had one or more of the underlying diseases, which was obesity, diabetic disease, hypertension, dyslipidemia, asthma/COPD. Meanwhile, 38 (50.67%) patients in the no storage symptoms group had one or more underlying

TABLE 1. Demographic data.

	Storage symptoms[1] (n=69)	No Storage symptoms[2] (n=67)	p-value
Age, year mean (SD)	36 (14)	33 (12)	0.221
Gender			
Male, n (%)	26 (42.62)	28 (37.33)	
Female, n (%)	35 (57.38)	47 (62.67)	0.598
Overall underlying disease			
Yes, n (%)	37 (60.66)	38 (50.67)	
No, n (%)	24 (39.34)	37 (49.33)	0.299
Obesity			
Yes, n (%)	28 (45.90)	39 (52.00)	
No, n (%)	33 (54.10)	36 (48.00)	0.864
Diabetic disease			
Yes, n (%)	5 (8.20)	10 (13.33)	
No, n (%)	56 (91.80)	65 (86.67)	0.416
Hypertension			
Yes, n (%)	5 (8.20)	10 (13.33)	
No, n (%)	56 (91.80)	65 (86.67)	0.416
Dyslipidemia			
Yes, n (%)	3 (4.92)	7 (9.33)	
No, n (%)	58 (95.08)	68 (90.67)	0.511
Asthma/COPD			
Yes, n (%)	1 (1.64)	3 (4.00)	
No, n (%)	60 (98.36)	72 (96.00)	0.628
Admitted ward			
ICU, n (%)	3 (4.92)	3 (4.0)	
Cohort, n (%)	32 (52.46)	21 (28.00)	
Field hospital, n (%)	26 (42.62)	51 (68.00)	0.007
Intravenous fluid therapy			
Yes, n (%)	3 (4.92)	3 (4.00)	
No, n (%)	58 (95.08)	72 (96.00)	1.000
Overall COVID-19 symptoms			
Asymptomatic, n (%)	10 (16.39)	26 (34.67)	
Symptomatic, n (%)	51 (83.61)	49 (65.33)	0.019
URI symptoms[2]			
Yes, n (%)	44 (72.13)	45 (60.00)	
No, n (%)	17 (27.87)	30 (40.00)	0.151
Fever			
Yes, n (%)	35 (57.38)	24 (32.00)	
No, n (%)	26 (42.62)	51 (68.00)	0.003

TABLE 1. Demographic data. (Continue)

	Storage symptoms[1] (n=69)	No Storage symptoms[2] (n=67)	p-value
Anosmia			
Yes, n (%)	11 (18.03)	10 (13.33)	
No, n (%)	50 (81.97)	65 (86.67)	0.482
Chest discomfort			
Yes, n (%)	11 (18.03)	10 (13.33)	
No, n (%)	50 (81.97)	65 (86.67)	0.482
Rash			
Yes, n (%)	2 (3.28)	1 (1.33)	
No, n (%)	59 (96.72)	74 (98.67)	0.587
Diarrhea			
Yes, n (%)	11 (18.03)	5 (6.67)	
No, n (%)	50 (81.97)	70 (93.33)	0.060
Pneumonia			
Absent, n (%)	26 (42.62)	17 (22.67)	
Present, n (%)	35 (57.38)	58 (77.33)	0.016

Abbreviation: SD: standard deviation, URI: respiratory tract infection.

[1] Storage symptom were defined as patients who had one or more symptoms of frequency voiding, urgency, urge incontinence, nocturia concomitant with OABSS score ≥ 1 during COVID-19 infection.

[2] Patients who did not develop any storage symptom during infection or had OABSS score 0 during COVID-19 infection.

[3] URI symptoms were defined as having one or more symptoms of cough, runny nose, sore throat, nasal congestion.

diseases, which was not statistically different between two groups. Most of the patients in the storage symptoms group (52.46%) were admitted to the cohort ward, in contrast to no storage symptoms group that most of the patients (68%) were admitted to the field hospital. Patients in the storage symptoms group were admitted to the cohort ward greater than the no storage symptoms group (52.46% VS 28.00%, p-value 0.007). There were only six patients who received intravenous fluid during admission, 3 patients in the storage symptoms group and 3 patients in the no storage symptoms group, which was not statistically different between the two groups.

Patients who had storage symptoms had statistically significantly COVID-19 symptoms greater than the no storage symptoms group (p-value 0.019). Moreover, fever and pneumonia were significantly related to storage symptoms (p-value <0.05). Although diarrhea was not statistically significant but it had the tendency to be related to storage symptoms (p-value 0.06)

From Table 2, Patients who had storage symptoms had an average daytime frequency higher than that of the no storage symptoms group, at 5.9 and 3.8 (p-value <0.001), respectively. Meanwhile, the number of nocturia were higher in who had storage symptoms, which were 2.0 and 1.0 (p-value <0.001). Patients who had storage symptoms had urgency significantly higher than no storage symptoms group (67.21% VS 6.67%, p-value <0.001). There were only 4 patients who had urge incontinence higher than in storage symptoms group but not statistically significant. Moreover, the OABSS and ICIQ storage subscale in the storage symptoms group were higher than no storage symptoms group, 3.2 VS 0.9 and 4.5 VS 1.7 (p-value < 0.001), respectively.

TABLE 2. Data of storage symptoms between two groups.

	Storage symptoms[1] (n=61)	No Storage symptoms[2] (n=75)	p-value
Daytime frequency, mean (SD)	5.9 (2.9)	3.8 (2.1)	< 0.001
Nocturnal frequency, mean(SD)	2.0 (1.2)	1.0 (1.2)	<0.001
Urgency			
Present, n (%)	41 (67.21)	5 (6.67)	
Absent, n (%)	20 (32.79)	70 (93.33)	<0.001
Urgency urinary incontinence during admission			
Present, n (%)	3 (4.92)	1 (1.33)	
Absent, n (%)	58 (95.08)	74 (98.67)	0.325
OABSS, mean (SD)	3.2 (2.2)	0.9 (1.0)	< 0.001
ICIQ (storage), mean (SD)	4.5 (2.7)	1.7 (2.3)	< 0.001

Abbreviation: SD: standard deviation, URI: respiratory tract infection, OABSS: overactive bladder symptom scores, ICIQ: International Consultation on Incontinence Modular Questionnaires.
[1] Storage symptoms were defined as patients who had one or more symptoms of frequency voiding, urgency, urge incontinence, nocturia concomitant with OABSS score ≥ 1 during COVID-19 infection.
[2] Patients who did not develop any storage symptom during infection or had OABSS score 0 during COVID-19 infection.

The factors associated with storage symptoms

From univariable analysis, the underlying diseases which were obesity, diabetes, hypertension, dyslipidemia, asthma and COPD were not associated with storage symptoms during COVID-19 infection. However, the symptoms and complication of the COVID-19 infection related to storage symptoms, particularly fever and pneumonia are significant related to storage symptoms but the URI symptoms, rash, anosmia and chest discomfort were not related to storage symptoms. After using the multivariable analysis factor associated with storage symptoms in COVID-19 patients by using the factors that would relate to storage symptoms, pneumonia is the only factor that was significantly related to storage symptoms in this study (OR 2.92 (1.04-8.21), p-value 0.042). Fever had a tendency to be related to storage symptoms but was not statistically significant (OR 2.12 (0.93-4.85), p-value 0.072) (Table 3).

TABLE 3. The Multivariable analysis factors associate with storage symptoms in COVID-19 patients.

Factor	Odd ratio (95% CI)[1]	p-value
Age in year	1.01 (0.98 - 1.04)	0.346
Male gender	1.24 (0.57 - 2.71)	0.584
Diabetic mellitus	0.34 (0.09 - 1.31)	0.119
Obesity	0.46 (0.19 - 1.13)	0.091
Fever	2.12 (0.93 - 4.85)	0.072
Pneumonia	2.92 (1.04 - 8.21)	0.042
Diarrhea	2.84 (0.79 - 10.15)	0.108

[1] The binary regression analysis was used for analyzing factors that associated with storage symptoms in COVID-19 infection patients.

The presence of leukocyte, hematuria or proteinuria related to the severity of COVID-19 infection and storage symptoms

From 136 COVID-19 patients, there were 34 patients who undertook the urine dipstick test. Even though they were not statistically significant, the patients who had abnormal urine dipstick tests were more likely to have more storage symptoms, fever, URI and pneumonia (Table 4).

DISCUSSION

The prevalence of the urinary storage symptoms in COVID-19 patients from our study population was 44.85%. Patients in the storage symptoms group had frequent voiding, urgency, nocturia, OABSS and ICIQ storage subscale significantly higher than the no storage symptoms group (p-value <0.001). The prevalence of these symptoms was quite high but there was no information about the abnormal storage symptoms to warn people that this might be a sign of COVID-19 infection. Similar to the previous studies[4,5], our study demonstrated that most COVID-19 patients could have more frequent voiding, nocturia and urgency during the infection. Patients in our study who had COVID-19 pneumonia were more likely to have abnormal storage symptoms than patients who had not. All patients were treated by conservative treatment which were prompt voiding, avoiding caffeine and adjusting fluid intake. None of these patients took medication or underwent any intervention to relieve symptoms.

The SAR-CoV-2 virus could be isolated from the urine sample. Hence, this virus would be contagious by urine.[3] The study by Kashi AH et al and Roshandel et al. demonstrated that the rate of SAR-CoV-2 viral shedding in urine was 1.18% and the detection rate of virus in urine was 4.5-8%. Even though the rate of shedding was lower than in nasopharyngeal and rectum, the viral shedding in urine was higher in patients who had greater severity of the disease and also related to higher mortality.[7,8] From our study, patients who had fever, diarrhea and pneumonia had a higher number of storage symptoms than the asymptomatic or mild symptoms group. Therefore, as well as showing storage symptoms of COVID-19 patients, the SAR-CoV-2 virus might also be transmitted to other people by urine contamination.

Currently, the pathophysiology of storage symptoms is still unclear. There are several mechanisms that could explain the storage symptoms. Firstly, the SAR-CoV-2 can transmit and replicate in the urothelial cells of the bladder via angiotensin converting enzyme 2 (ACE2) receptors in the viremia stage and result in viral cystitis.[9,10] Secondly, the SAR-CoV-2 virus can cause endothelitis which could irritate bladder and result in storage symptoms. Lastly, the SAR-CoV-2 virus can cause inflammation from immunologic response as a previous study found inflammatory cytokine IL-6, IL-8, IP-10 increase in urine

TABLE 4. The presence of leukocyte, hematuria or proteinuria related to the severity of COVID-19 infection and storage symptoms.

Symptoms	Abnormal urine dipstick[1](25)	Normal urine dipstick(9)	p-value
Storage symptoms[2], n (%)	14 (56.00)	3 (33.33)	0.438
Frequency, n (%)	11 (44)	2 (22.22)	0.427
Urgency, n (%)	7 (28)	3 (33.33)	1.000
Daytime frequency, mean (SD)	4.7 (3.1)	4.4 (3.3)	0.823
Nocturia, mean (SD)	1.8 (1.4)	1.2 (0.6)	0.241
Fever, n (%)	7 (28)	2 (22.22)	1.000
URI[3], n (%)	11 (44)	6 (66.67)	0.438
Pneumonia, n (%)	2 (8)	1 (11.11)	1.000

Abbreviation: SD: Standard deviation, URI: upper respiratory tract infection.
[1] abnormal urine dipstick was defined by positive for any of the following, leukocyte, hematuria, or proteinuria.
[2] Storage symptom was defined as patients who voided more frequently or had urgency symptom during COVID-19 infection.
[3] URI symptoms were defined as having one or more symptoms of cough, runny nose, sore throat, nasal congestion

of COVID-19 patients and these patients had urgency, frequency and nocturia.[11]

The limitation of our study was that this study was carried out as a cross-sectional study because it was difficult to communicate with patients and collect the data during this severe pandemic situation. Therefore, we cannot identify the true causal relation of the risk factors associated to abnormal storage symptoms. We could simply imply the probability of the factors that might be related to storage symptoms from the high rate of concomitance with the storage symptoms during the illness as the prediction model of the study. To identify the true effect of the factors, a cohort study could be undertaken in the future. Moreover, we did not collected the data about the frequency of voiding and nocturia before infection because from our pilot study, most of the patients were not willing to answer too many questions and most of them could not remember. In order to avoid recall bias and disturb patients during their illness, therefore, we did not collect the data before the illness. Another limitation of our study was we could not follow up the symptoms of patients after recovery from the illness because of limited access to the contact information of the patients after they went home. However, the study by Welk et al. reported that COVID-19 patients who had storage symptoms during illness did not have increased risk of long term bladder dysfunction.[12]

From our study, underlying disease, which were obesity, diabetes, hypertension, dyslipidemia, and asthma/COPD were not significantly related to storage symptoms. Most of the patients who had storage symptoms were admitted to the cohort ward (52.46% VS 28%, p-value 0.007). This data was coherent with the data regarding COVID-19 symptoms in patients who had fever and pneumonia were statistically significantly related to storage symptoms. These might occur because most of the patients who had pneumonia and more severe disease were admitted to the cohort ward. However, apart from the viral cystitis from the COVID-19 infection that resulted in storage symptoms, there were many factors that might also be related to storage symptoms, for example, resulting from increasing fluid intake during illness, anxiety or cold temperature of the air conditioning room, glucosuria in diabetic patients.[5] Generally, patients who were admitted to ICU might be affected from the intravenous fluid, colder temperature than cohort ward and field hospital that could cause storage symptoms such as frequency urination. Even though our study demonstrated that intravenous fluid was not associated with storage symptoms, there were only 6 patients who were admitted to ICU, therefore the sample size of this group was too small to conclude the association between ICU patients and storage symptoms in this study. None of the patients in this study received a bronchodilator.

From multivariable analysis, only pneumonia was significantly associated with storage symptoms (p-value 0.042). Fever had a tendency to be related to storage symptoms but was not statistically significant. These might be because patients who had fever not only had involvement from viral cystitis but also affected from increased fluid intake and cold temperature of the air conditioning room.

Rui Liu et al. found red blood cell and proteinuria are significantly higher in COVID-19 patients. Patients who had glucosuria or proteinuria were more likely to have more severe COVID-19 disease.[13] From our study, even though there they were not statistically significantly different, the patients who had leukocyte, erythrocyte or proteinuria positive from the dipstick test tended to have more storage symptoms and more fever, URI, and pneumonia.

Regarding the information from our study and previous studies, medical personnel, especially urologists and general physicians, should be aware that the patients who were infected by SARS-CoV-2 virus might present at the hospital with abnormal storage symptoms and abnormal urinalysis that mimic the urinary tract infection. Moreover, in order to increase the awareness of carrying the disease and risk of transmitting the virus to others, people should know that storage symptoms could also be the symptoms of the COVID-19 virus.

CONCLUSION

Our study demonstrated that SARS-CoV-2 virus infection in patients who had pneumonia and fever was associated with abnormal storage symptoms, including frequency, urgency and nocturia. These storage symptoms may be related to the severity of COVID-19 disease. Patients and medical personnel should be aware that storage symptoms might be found together with fever and pneumonia as well as presenting symptoms of COVID-19.

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Conflict of interest
We have no conflict of interest.

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