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Long COVID and COVID-19-associated cystitis (CAC)

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Abstract

Purpose There is scarce literature regarding genitourinary symptoms in COVID-19, especially post-acute disease otherwise known as Long COVID. We identified recovered COVID-19 patients presenting with new or worsening overactive bladder symptoms, known as COVID-19-associated cystitis (CAC).

Methods We used the American Urological Association Urology Care Foundation Overactive Bladder (OAB) Assessment Tool to screen COVID-19 recovered patients presenting with urological complaints at our urban-located institution from 5/22/2020 to 12/31/2020. Patients 10–14 weeks post-discharge responded to 5 symptom and 4 quality-of-life (QoL) questions. We reported median symptom scores, as well as QoL scores, based on new or worsening urinary symptoms, and by sex.

Results We identified 350 patients with de novo or worsening OAB symptoms 10–14 weeks after hospitalization with COVID-19. The median total OAB symptom score in both men and women was 18. The median total QoL score for both men and women was 19. Patients with worsening OAB symptoms had a median pre-COVID-19 symptom score of 8 (4–10) compared to post-COVID-19 median symptom score of 19 (17–21). Median age was 64.5 (range 47–82). Median hospital length-of-stay was 10 days (range 5–30).

Conclusion We report survey-based results of patients suffering from new or worsening OAB symptoms months after their hospitalization from COVID-19. Future studies with larger sample sizes and more extensive testing will hopefully elucidate the specific pathophysiology of OAB symptoms in the context of long COVID so urologists can timely and appropriately treat their patients.

Keywords COVID-19 · Bladder · SARS-CoV-2 · Overactive bladder · Long COVID · COVID-19-associated cystitis

Introduction

Common symptoms in Coronavirus Disease 2019 (COVID-19), the disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), have been well-reported and can include fever, dry cough, difficulty breathing, and tiredness. Although many patients infected with the virus develop mild symptoms, a small percentage of individuals can progressively develop acute respiratory distress syndrome and ultimately multiple organ dysfunction syndrome resulting in demise [1]. Additionally, there is an emergence of patients who experience new symptoms that involve nearly all organ systems, some more subtle than others. As these symptoms may overlap with other common disease processes and due to the preponderance of retrospective observational population studies, it has been difficult to establish any causation links between the various symptoms and COVID-19 as the underlying cause [2].

Although less-identified, but becoming increasingly reported, are patients with COVID-19 developing new onset or an exacerbation of baseline urinary symptoms, most notably overactive bladder (OAB) [3, 4]. This has been referred to as COVID-19-associated cystitis (CAC) [5, 6]. The underlying pathophysiology of urinary symptoms in COVID-19 patients is not clearly understood but hypotheses have

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begun to emerge from smaller, single-center studies [3, 5, 6] which are currently elucidating the impact of COVID-19 on the genitourinary system. Furthermore, whether urinary symptoms and any associated bother occur in long COVID or post-acute COVID-19 syndrome (PACS) patients has not been thoroughly investigated. In our study, we identified confirmed COVID-19 patients who also showed new or worsening urinary symptoms consistent with OAB 10–14 weeks after hospital discharge. Our aim is to find an association between the urinary symptoms, notably OAB, and COVID-19 using questionnaires.

Methods

This study had full IRB approval from Wayne State University's IRB (IRB#20–04-2126-M1) and full written consent was provided by all research participants. Patients were admitted to Detroit Medical Center (Detroit, MI) for treatment of COVID-19 and discharged. Discharged patients who complained of urological symptoms were referred for urology follow-up and surveyed regarding their current urinary symptoms, and if applicable, how their symptoms changed after recovering from COVID-19. This was done in an office setting during a scheduled appointment 10–14 weeks post-discharge. Respondents were informed that they would be asked questions regarding their urinary wellness, in addition to information regarding age, race, history of OAB or benign prostatic hyperplasia (BPH), and current medications to control urinary symptoms. When possible, the patient's hospital admission and discharge dates were confirmed to establish length-of-stay (LOS). Patients were given the option to decline participation or stop the survey at any time. Responses were collected from 5/22/2020 to 12/31/2020.

Our primary outcome variable was the American Urological Association's Urology Care Foundation Overactive Bladder Assessment Tool (Supplemental Table 1) [7]. The five individual symptom scores for frequency (range from 0 to 5; 0 being 'not at all' and 5 being 'almost always') of the following symptoms: urgency, urge incontinence, incontinence, frequency, and nocturia. The total symptom score ranges from 0 (no symptoms) to 25 (most severe symptoms). Additionally, there are four QoL questions regarding symptom bother (range from 0 to 5; 0 being 'I am not bothered at all' and 5 being 'I am bothered a great deal') for urgency, urge incontinence, frequency, nocturia, and overall satisfaction with their current urinary condition. This score ranged from 0 representing "not bothered at all" to 5 representing "bothered a great deal". Patients with history of OAB symptoms were asked to score their pre-COVID-19 symptoms compared to post-COVID-19 symptoms. Lastly, a final QoL question asks, 'How have your symptoms changed your life?' Patients could then select all of the eight associated questions pertaining to specific life activities that are affected by their OAB (e.g. Keeping you from getting a good night's sleep?; Causing you to stay home more than you would like?; Causing you to exercise less or limit your physical activity?; Causing problems with friends or loved ones?; Keeping you from social activities or entertainment?; Keeping you from traveling, taking trips, or using public transit?; Making you plan trips around your knowledge of public restroom location?; Causing problems at work?), including a free-response option.

Table 1 Demographics of study population

	N
Participants	350
Age median (range)	64.5 (47–82)
Gender	
Female (%)	140 (40%)
Male (%)	210 (60%)
Ethnicity	
Black (%)	305 (87%)
White (%)	45 (13%)
Onset	
New (%)	250 (71%)
Worsening (%)	100 (29%)
BPH (% male population)	110 (52%)

Results

Demographics

We identified 350 confirmed COVID-19 patients, including 140 females and 210 males, who developed either new or worsening symptoms associated with OAB 10–14 weeks following SARS-CoV-2 infection (Table 1). These were all patients that were referred to a urologist post-discharge due to their urology symptoms. There were 100 patients with prior OAB history, while 250 presented with new-onset OAB symptoms. The median age of patients was 64.5 years old (range 47–82 years old). Median LOS was 10 days (range 5–30 days). The majority of the COVID-19 patients identified as black ($n = 305$; 87%), as expected for the clinical population of this medical system (Table 1). BPH was identified in 110 men (52.4% of all males).

Outcomes

All 350 patients completed the symptom score and QoL surveys (Supplemental Table 1). The median total OAB symptom score in both men and women was 18 (ranges 12–20 and 15–21, respectively). In patients with new onset

OAB symptoms, the median symptom score was 18 (12–21), while patients with worsening OAB symptoms had a median pre-COVID-19 symptom score of 8 (4–10) compared to post-COVID-19 median symptom score of 19 (17–21). The median QoL score for both men and women was 19 (16–20 and 16–21, respectively). In patients with new onset OAB symptoms, the median QoL score was 19 (16–24). In patients with worsening OAB, median pre-COVID-19 QoL score was 9 (8–10) compared to median post-COVID-19 QoL score of 20 (19–20). All patients indicated nocturia had impacted their QoL. Primary outcomes are reported in Table 2.

Discussion

The results of the present investigation bring awareness to symptoms of OAB in recovered COVID-19 patients and the gaps in knowledge hereby identified. Symptoms of OAB are an important factor in patients' QoL, but one that can be addressed when identified in a timely manner. In our cohort, the temporal aspect with the change in urinary symptoms suggests an impact from COVID-19 and a possible symptom to be included in long COVID or post-acute COVID-19 syndrome (PACS). Although causation cannot be established, several possibilities are currently considered. The pathophysiology of SARS-CoV-2 involves the binding of the viral spike protein to angiotensin converting enzyme 2 (ACE2) receptors located on pneumocytes, but are also present in the bladder and other organs [8]. It is therefore plausible that the de novo or worsening OAB symptoms observed in the current study are a downstream effect of cellular cascade resulting from activation of the bladder specific ACE2 receptors. SARS-CoV, a related virus, has been found to be shed in the urine [9], however, SARS-CoV-2 has been reported by multiple groups to only be detectable in a small subset of COVID-19 patients by molecular detection [10–13] or detection of the spike protein [14]. Another hypothesis in the literature suggests a direct insult to the bladder or urothelium causing viral cystitis [3]. Lastly, increased pro-inflammatory cytokines have been detected in COVID-19 patients with de novo severe urinary symptoms, suggesting that COVID-19 associated inflammation may result in bladder dysfunction [6]. Future studies are needed to clarify if these symptoms are associated with alterations in bladder pathology.

Other viruses, including human immunodeficiency viruses (HIV) that can lead to acquired immunodeficiency syndrome (AIDS), are known to cause bladder control issues. In HIV, the underlying cause of urinary symptoms includes opportunistic pathogens (i.e. toxoplasmosis) as well as direct neurogenic insult from the virus itself. HIV has the potential to cross the blood–brain-barrier and causes various peripheral neurologic diseases, and studies of HIV/AIDS patients confirmed neurogenic bladder as the culprit through urodynamic testing [15, 16]. Although data are preliminary, there is evidence that infection with SARS-CoV-2 can lead to neurocognitive symptoms post-infection, possibly due to insult to the nervous system [17].

This study is the first to look at lower urinary tract symptoms by survey consistent with OAB in a large cohort of patients recovering from COVID-19 after hospitalization. All these patients were referred to urology for follow-up. Interestingly, 71% of patients reported new onset of urinary symptoms after COVID-19 infection, and 29% of patients who had previous OAB symptoms reported worsening of their symptoms after COVID-19 infection. Given that all these patients were hospitalized for COVID-19, these findings may be representative of those patients who had severe acute disease and may not be seen in COVID-19 patients that had asymptomatic, mild, or moderate disease not requiring hospitalization. Our cohort was primarily composed of elderly patients, who often have pre-existing genitourinary (GU) symptoms, and therefore presents a confounding variable in the study. However, this is consistent with a prospective study where lower urinary tract symptoms (LUTS) were increased in elderly men during COVID-19 hospitalization as measured by the International Prostate Symptom Score (IPSS) [18]. Future studies will evaluate GU symptoms in younger adult patients to see if this is related to age in addition to SARS-CoV-2 infection, and at later time points post SARS-CoV-2 infection. A smaller study comprised of younger patients (mean and standard deviation of age of female and male patients was 32.3 ± 8.9 and 38.9 ± 13 years old, respectively) found that LUTS, especially storage symptoms, were more prevalent during acute COVID-19 [19]. Our cohort demographic was primarily composed of patients identifying as Black, which is expected given our urban location and typical clinical population. While COVID-19 has been reported to disproportionately impact Black and Hispanic/Latino populations [20], other studies have demonstrated that there is no difference by race for in-hospital mortality, intubation, or ICU days [21–23] and that socioeconomic vulnerability, independent of race, predicted in-hospital mortality

Table 2 Primary outcomes for symptom & quality-of-life scores

Classification (n)	Symptom score (Median)	Range	QoL score (Median)	Range
New ($n=250$)	18	12–21	19	16–24
Worsening ($n=100$)				
Before COVID-19	8	4–10	9	8–10
After COVID-19*	19*	17–21*	20*	19–20*
Female ($n=140$)	18	15–21	19	16–21
Male ($n=210$)	18	12–20	19	16–20

*Only "After COVID-19" symptom scores for patients with preexisting OAB are included in the male/female analysis

[22, 23]. The cohort was also recruited from a urology clinic and therefore more likely to report GU symptoms regardless of COVID-19 status. Even though they had not previously reported OAB symptoms until after hospitalization, 21 men were previously confirmed to have BPH, which may have had confounding effects in the development of their symptom post-COVID-19. A report by Luciani et al. suggests that the urinary tract was severely impacted in three men with symptomatic COVID-19 infection during hospitalization that had a history of previous urological conditions (i.e. BPH and radiation cystitis); the authors hypothesize that the previous urological conditions made the patients especially vulnerable to damage to the urinary tract by COVID-19, including hematuria [24]. Interestingly, Welk and colleagues have reported that there was no increase in urology consultation, cystoscopy, or overactive bladder medication prescription among patients who had COVID-19, compared to the matched cohort [25]. However, their study was limited in that it did not contain patient reported outcome measures, or direct measures of urinary symptoms. It is possible that their patient population did not seek medical care or receive treatment related to their urologic symptoms during the time period studied. Furthermore, their study investigated all patients who had a positive nasopharyngeal swab for SARS-CoV-2, whereas this study was focused only on patients who were hospitalized for COVID-19 and referred to urology. One limitation of our study is the lack of a comparison group of OAB patients that were COVID-19 negative to see if their OAB symptoms changed during the same time frame in response to pandemic related stress or changes in lifestyle.

Currently, it is not clear if symptoms of OAB in the setting of COVID-19 are reversible or irreversible without longer follow-up. Future testing, including urodynamic studies, could help determine the underlying pathophysiology. Ultimately, future prospective multi-center studies with long-term follow-up are necessary to address these issues. The findings of our study indicate that worsening or de novo urinary symptoms in COVID-19 patients may be secondary to the disease. Most importantly, management of the urinary symptoms in COVID-19 recovered patients may be possible with medications and surgical interventions; these treatments may differ from those indicated for patients not affected by COVID-19. Therefore, it may be important to differentiate the diagnosis as either an independent urinary disease or as a sequela of COVID-19.

Conclusion

We report survey-based results of a cohort of 350 patients suffering from new or worsening OAB symptoms 10–14 weeks after their hospitalization from COVID-19. This supports that urinary urgency, frequency, and nocturia can be long COVID-19 symptoms that can significantly impact a patient's QoL. Future prospective, multi-center studies will be necessary to elucidate the specific pathophysiology of OAB symptoms in the context of COVID-19 such that urologists can appropriately treat these patients in a timely fashion.

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Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no relevant conflict of interest to report.

Ethical approval This study involving human participants was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional review board of Wayne State University (IRB#20-04-2126-M1) approved this study. Informed consents were obtained from all research participants.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of their data.

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