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ORIGINAL RESEARCH

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How different strains of COVID-19 affect LUTS in BPH patients?

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Abstract

In late 2019, an outbreak of pneumonia of unknown etiology was reported in Wuhan (China). The causative agent was quickly identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the impact of COVID-19 (coronavirus disease 2019) on various organs and symptoms has been studied, there is still a dearth of data regarding its effect on the genitourinary system. In this study, we investigated the impact of different COVID-19 strains on lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH). A total of 69 patients who had previously been infected with COVID-19 from August 2021 to October 2021 and January 2022 to May 2022 were assessed. The two periods were purposively selected based on the dominant COVID-19 variant: the Delta strain for the first period and Omicron for the second, respectively. All patients had BPH and were followed up in two outpatient practices. Demographic information was collected, and LUTS were assessed using the international prostate symptom score (IPSS) questionnaires before and after COVID-19. Ultrasound examinations were performed to determine the prostate gland volume and the post-voided residual (PVR) in each patient. All patients affected by COVID-19 exhibited a worsening of LUTS. The degree of deterioration differed between those infected with different COVID-19 strains. Patients infected with the Delta strain had more severe LUTS than those with the Omicron strain. There is currently limited information available regarding the emerging pathophysiological processes in the urogenital system related to COVID-19. This present study serves as a preliminary investigation into the impact of COVID-19 on LUTS in BPH patients and could serve as a basis for more extensive multicenter studies leading to fundamental discoveries.

Keywords

COVID-19; BPH; LUTS; Strains

1. Introduction

At the end of 2019, the city of Wuhan (China) experienced an outbreak of pneumonia of an unknown causative agent [1]. Soon after several cases started to emerge, the agent was identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2], and the World Health Organization defined the resulting disease as the coronavirus disease 2019 (COVID-19) [3]. On 11 March 2020, the World Health Organization publicly declared COVID-19 a pandemic [4], quickly becoming one of the biggest public health threats. Beyond its health aspects, COVID-19 has also impacted many other areas of public life, including economics, social dynamics, culture and more. The disease has since manifested in multiple waves worldwide, with each wave characterized by a specific viral strain (Alpha, Beta, Gamma, Delta, Omicron). The first wave occurred in spring 2020, the second in late summer and autumn 2020, the third in early 2021 and the fourth in late 2021 and early 2022.

The entry of SARS-CoV-2 into cells relies on the key entry molecules ACE2 (Angiotensin-converting enzyme 2) and TMPRSS2 (Transmembrane serine protease 2) molecules, key players in cellular infection development [5]. The clinical manifestations of COVID-19 infection typically involve respiratory symptoms (*i.e.*, cough, fever, *etc.*), with advanced cases often complicated by acute respiratory distress syndrome (ARDS) due to cytokine storms and associated with high mortality rates [6].

Benign prostatic hyperplasia (BPH) is a socially significant disease marked by an increase in the volume of the prostate gland, leading to obstruction and reduced urine flow [7]. The clinical manifestation of BPH is assessed using the International Prostate Symptom Score (IPSS), a questionnaire that includes information on lower urinary tract symptoms (LUTS) and quality of life (QoL) [8].

With new developments in understanding the COVID-19 pandemic, numerous extrapulmonary tissues affected during the development of the infection have been identified, includ-

ing the gastrointestinal, urogenital, cardiovascular and nervous system [9]. However, impact data and research on the impact of COVID-19 on symptoms and organs of the genitourinary system remains limited.

This knowledge gap prompted us to investigate the impact of different strains of COVID-19 on LUTS in patients with BPH.

2. Materials and methods

The present study comprised 69 patients with a past history of infection of COVID-19 in the two following periods: August–October 2021 and January–May 2022. These two periods were purposively selected given the dominant variant of the COVID-19 infection: Delta strain for the first period and Omicron for the second, respectively.

All patients were followed up for BPH in two outpatient practices and underwent medical treatment with an alpha-blocker, a 5-alpha reductase inhibitor or a combination drug. Patients with an indwelling urethral catheter, existing urinary tract infection, and past BPH surgery were excluded from the study. The demographic information of the cohort was analyzed and systematized.

LUTS were assessed using IPSS questionnaires completed before and after COVID-19. The follow-up period for all the patients was 9 months. All the patients continued their therapy for BPH during COVID treatment and in the follow-up period. Information on the volume of the prostate gland and the post-voided residual (PVR) was derived from ultrasound examination. The study was conducted following the ethical principles of the Declaration of Helsinki.

All statistical results were processed using the SPSS (Statistical Package for the Social Sciences) Statistics v26 (IBM, Armonk, NY, USA) and their graphic presentation using Microsoft Excel 2019 (Microsoft, Redmond, Washington, USA). All numeric variables were tested for normal distribution using the Kolmogorov-Smirnov test. Descriptive statistics, nonparametric tests, *t*-test, one-way analysis of variance (ANOVA) and Bonferroni post-hoc test were used during statistical analyses. A $p < 0.05$ was adopted for all tests to determine statistical significance.

3. Results

The data of 69 patients were assessed for this study. Of them, 52% (n = 36) were infected by the Omicron strain and 47.2 $\pm$ 6.0% with the Delta strain. The mean age and mean body mass index (BMI) of the patients were 66.5 $\pm$ 0.9 years and 25.2 $\pm$ 1.6 kg/m^2, respectively. A significant difference was observed between the two groups of patients regarding the type of treatment ($p > 0.05$), whereby 45.5% of individuals infected with the Delta variant were admitted to the hospital for treatment, compared to only 27.8% of those with the Omicron variant. Conversely, no significant difference was observed regarding BPH therapy between the two groups ($p > 0.05$) (Table 1).

The data obtained from the completed IPSS questionnaires and the performed ultrasound examination of the patients from both groups were subjected to comparative analysis and the results are shown in Tables 2 and 3.

The overall results obtained from both groups of patients revealed a statistically significant increase in all the investigated indicators ($p < 0.05$).

Notably, a significant difference was observed in the rate of increase in IPSS between the Delta and Omicron groups, with the former exhibiting a more than 2-fold increase (from 7.8 before COVID-19 to 15.5 after COVID-19) compared to the latter (from 11.2 to 13.2, respectively) ($p < 0.000$). No statistically significant difference was observed between the two groups of patients concerning an increase in prostate volume and PVR ($p > 0.05$). In terms of QoL, a reciprocal trend of changes in IPSS was observed between the Delta and Omicron groups. Specifically, a more than 2-fold decrease in the quality of life of patients was noted in the Delta group (from 2.0 before COVID-19 to 4.5 after COVID-19) ($p < 0.000$), whereas a significantly lower QoL violation in patients from the Omicron group (from 2.3 before to 2.8 after COVID-19) ($p = 0.003$). Importantly, no complications such as urinary retention or incontinence were observed in both groups.

4. Discussion

Since its emergence in late 2019, SARS-CoV-2 has posed an unprecedented challenge for health authorities worldwide [4]. Its predominant symptoms include cough, fatigue, fever, *etc*. [10]. The characteristic shape of the virus is attributed to its membrane spike-proteins [11], which facilitate viral entry into host cells by binding to angiotensin-converting enzyme 2 (ACE 2) receptors located on the cell surface. For the fusion process of the cell and viral membrane to be successful, it is necessary to cleave the spike proteins, a process facilitated by transmembrane serine protease 2 (TMPRSS2) [5]. Apart from its role in the pathogenesis of COVID-19, this protease is also involved in regulating prostate cancer processes [12]. It is highly expressed in prostatic epithelial cells, with particularly high levels of expression seen in cases of high Gleason prostate carcinoma [13]. Zou *et al*. [14] reported high ACE2 expression in kidney proximal tubule cells (4%) and bladder urothelial cells (2.4%). In another study, Ren *et al*. [15] reported high ACE2 and TMPRSS2 expression levels in kidney and testicular tissues.

Mumm *et al*. [16] reported increased urinary frequency in 7 of 57 patients with COVID-19, suggesting that this was due to preexisting viral cystitis. Dhar *et al*. [17] presented data on de novo LUTS in patients positive for COVID-19. Can *et al*. [18] conducted a study to investigate the impact of COVID-19 infection on lower urinary tract symptoms (LUTS) in patients over 50 years old. The authors compared the International Prostate Symptom Score (IPSS) before and during acute COVID-19 infection and found a statistically significant difference between IPSS before and during COVID-19 infection (5.1 $\pm$ 4.1 versus 9 $\pm$ 6.4; $p < 0.001$) [19]. In a separate study by Sevim *et al*. [19], data from 142 patients with benign prostatic hyperplasia (BPH) who were hospitalized due to COVID-19 were analyzed. The authors observed an increase in IPSS from the beginning of hospitalization to 1 month after recovery from the virus (IPSS: 10.7 $\pm$ 4.5 to 12.9 $\pm$ 3.6; $p < 0.01$) and QoL (2.5 $\pm$ 0.6 to 2.8 $\pm$ 0.5; $p < 0.01$). Additionally, they noted a progression in urinary frequency and nocturia

TABLE 1. Patients' demographics.

Variable	Delta type			Omicron type			F	*p*
	n	mean	std. error	n	mean	std. error		
Age	33	66.4	1.2	36	66.6	1.2	0.02	0.901
BMI	33	25.3	1.3	36	25.6	1.3	0.01	0.857
	n	%	Sp (%)	n	%	Sp (%)	χ^2	*p*
Treatment								
home	18	54.5	8.7	26	72.2	7.5	2.33	0.127
hospital	15	45.5	8.7	10	27.8	7.5		
Treatment BPH								
alpha-blocker	17	51.5	8.7	17	47.2	8.3		
5α-reductase inhibitor	7	21.2	7.1	8	22.2	6.9	0.14	0.934
combine	9	27.3	7.8	11	30.6	7.7		

BMI, body mass index; BPH, benign prostatic hyperplasia.

TABLE 2. Objective parameters of the Delta strain group (before and after COVID-19).

Delta type								
Variable	Before COVID-19 treatment			After COVID- 19 treatment			t	*p*
	n	mean	std. error	n	mean	std. error		
IPSS	33	7.8	0.6	33	15.5	0.8	12.47	<0.000
Prostate volume	33	63.4	3.1	33	64.1	3.2	2.48	0.018
PVR	33	14.3	2.4	33	24.6	3.9	3.37	0.002
QoL	33	2.0	0.2	33	4.5	0.2	12.14	<0.000

COVID, coronavirus disease; IPSS, international prostate symptom score; PVR, post-voided residual; QoL, quality of life.

TABLE 3. Objective parameters of the Omicron strain group (before and after COVID-19).

Omicron type								
Variable	Before COVID-19 treatment			After COVID- 19 treatment			t	*p*
	n	Mean	Std. Error	n	Mean	Std. Error		
IPSS	36	11.2	0.9	36	13.2	0.9	5.13	<0.000
Prostate volume	36	68.2	3.9	36	69.2	3.9	3.43	0.002
PVR	36	24.6	3.5	36	33.9	4.3	3.45	0.002
QoL	36	2.3	0.2	36	2.8	0.3	3.23	0.003

COVID, coronavirus disease; IPSS, international prostate symptom score; PVR, post-voided residual; QoL, quality of life.

[19]. Nabeeh *et al*. [20] observed a significant increase in IPSS in 50 patients with BPH and COVID-19 during their hospital stay and 1 month and 3 months post-hospitalization (26.6 $\pm$ 5.8; 25.4 $\pm$ 5.86; 25.1 $\pm$ 6.3) compared with IPSS before infection (13.4 $\pm$ 4.3 $p < 0.001$). Regarding QoL, the authors also noted a significant deterioration from 3.4 $\pm$ 1.0 before the illness from COVID-19 to 5.3 $\pm$ 0.7 ($p < 0.001$) after recovery [20]. Further, Lamb *et al*. [21] divided 8 patients into two groups (4 patients with de novo LUTS and proven COVID-19 infection and 4 without LUTS and COVID-19) and examined the levels of pro-inflammatory cytokines in their urine. In patients from the first group, significantly higher levels of IL-6 (interleukin-6) ($p = 0.046$) and IL-8 ($p = 0.002$) were observed compared to those in the second group [21].

Overall, our present study showed a statistically significant increase in IPSS, prostate volume, PVR and QoL before and after COVID-19 ($p < 0.05$).

The first case of the COVID-19 Delta strain was reported in October 2020. It is characterized by a higher frequency of transmissibility and infectivity than all variants of the virus known to date [22]. On 09 November 2021, the first case of the Omicron strain was reported [23]. Related studies have established the Omicron strain infection has a much milder disease course [24]. Fisman *et al*. [25] reported that patients with the COVID-19 Delta variant had an increased risk of hospitalization (OR (odds ratio) 2.1 (95% CI (confidence interval) 1.8–2.4)), intensive care unit treatment (OR 3.4 (95% CI 2.6–4.3)) or death (OR 2.3 (95% CI 1.5–3.3)). It has been observed in various studies that the COVID-19 Omicron variant has a much weaker disease development compared to

other known variants.

Our findings suggest a less pronounced elevation of IPSS in the Omicron cohort, while patients infected with the Delta variant experienced a more significant decline in their quality of life.

However, our study had several limitations, including a relatively small number of patients due to some restrictions and patient-related factors, as well as the lack of laboratory investigations (patients were followed-up in outpatient settings) and functional diagnostics such as uroflowmetry.

5. Conclusions

The elucidation of the underlying mechanisms *via* which COVID-19 induces various urinary system disorders and the identification of associated risk factors has been beneficial in developing therapeutic strategies aimed at mitigating the occurrence of urological complications. To date, information on the emerging pathophysiological processes in the urogenital system remains limited. Altogether, this present study serves as a foundation for more in-depth multicenter studies, which may lead to fundamental and transformative discoveries in this field.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

AI and PA—Conceptualization, investigation, resources. AI—methodology, writing-original draft preparation. EA—software, data curation. AI, PA and PU—validation. GR—formal analysis, project administration. PA—writing-review and editing, supervision, funding acquisition. PU—visualization. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study design was constructed in order to the ethical principles of the Declaration of Helsinki. Ethics approval was not required for this study in accordance with local/national guidelines. Informed consent was obtained from all subjects involved in the study. Written informed consent was obtained from the patients regarding using the data for academic publications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. Journal of Travel Medicine. 2020; 27: taaa008.

[2] Gorbalenya AE, Baker SC, Baric RS, Groot RJ, Drosten C, Gulyaeva A, *et al*. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology. 2020; 5: 536–544.

[3] World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report—22. 2020.

[4] Ebrahim SH, Ahmed QA, Gozzer E, Schlagenhauf P, Memish ZA. COVID-19 and community mitigation strategies in a pandemic. BMJ. 2020; 368: m1066.

[5] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181: 271–280.e8.

[6] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020; 395: 507–513.

[7] Roehrborn CG. Benign prostatic hyperplasia: an overview. Reviews in Urology. 2005; 9: S3–S14.

[8] Gratzke C, Bachmann A, Descazeaud A, Drake MJ, Madersbacher S, Mamoulakis C, *et al*. EAU guidelines on the assessment of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European Urology. 2015; 67: 1099–1109.

[9] Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al*. Extrapulmonary manifestations of COVID-19. Nature Medicine. 2020; 26: 1017–1032.

[10] Perlman S. Another decade, another coronavirus. The New England Journal of Medicine. 2020; 382: 760–762.

[11] Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. Nature Reviews Molecular Cell Biology. 2022; 23: 3–-20.

[12] Afshari A, Janfeshan S, Yaghobi R, Roozbeh J, Azarpira N. COVID-19 pathogenesis in prostatic cancer and TMPRSS2-ERG regulatory genetic pathway. Infection, Genetics and Evolution. 2021; 88: 104669.

[13] Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, *et al*. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discovery. 2014; 4: 1310–1325.

[14] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Frontiers of Medicine. 2020; 14: 185–192.

[15] Ren X, Wang S, Chen X, Wei X, Li G, Ren S, *et al*. Multiple expression assessments of ACE2 and TMPRSS2 SARS-CoV-2 entry molecules in the urinary tract and their associations with clinical manifestations of COVID-19. Infection and Drug Resistance. 2020; 13: 3977–3990.

[16] Mumm J, Osterman A, Ruzicka M, Stihl C, Vilsmaier T, Munker D, *et al*. Urinary frequency as a possibly overlooked symptom in COVID-19 patients: does SARS-CoV-2 cause viral cystitis? European Urology. 2020; 78: 624–628.

[17] Dhar N, Dhar S, Timar R, Lucas S, Lamb LE, Chancellor MB. *De novo* urinary symptoms associated with COVID-19: COVID-19-associated cystitis. Journal of Clinical Medicine Research. 2020; 12: 681–682.

[18] Can O, Erkoç M, Ozer M, Karakanli MU, Otunctemur A. The effect of COVID-19 on lower urinary tract symptoms in elderly men. International Journal of Clinical Practice. 2021; 75: e14110.

[19] Sevim M, Alkiş O, Kartal İG, Coşer Ş, Akman H, Aras B. Impact of COVID-19 on the progression of benign prostatic hyperplasia and

aggravation of related symptoms: a prospective study. The Prostate. 2023; 83: 82–86.

[20] Nabeeh H, Ibrahim A, Taha DE, Talaat M, Abdelbaky TM. Impact of COVID-19 pandemic on lower urinary tract symptoms in patients with benign prostatic hyperplasia and predictors of urine retention in such patients. Lower Urinary Tract Symptoms. 2022; 14: 41–46.

[21] Lamb LE, Dhar N, Timar R, Wills M, Dhar S, Chancellor MB. COVID-19 inflammation results in urine cytokine elevation and causes COVID-19 associated cystitis (CAC). Medical Hypotheses. 2020; 145: 110375.

[22] Lal A, Ahmed N, Maqsood A, Alam MK. COVID-19 omicron-another deadly dilemma. Altamash Journal of Dentistry and Medicine. 2022; 1: 1–5.

[23] World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. 2021. Available at: https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern (Accessed: 03 December 2021).

[24] Khan K, Karim F, Cele S, San JE, Lustig G, Tegally H, *et al*. Omicron infection enhances neutralizing immunity against the Delta variant. medRχiv. 2022. [Preprint].

[25] Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. CMAJ. 2021; 193: E1619–E1625.

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