MANAGEMENT OF COVID-19 EFFECTS ON LOWER URINARY TRACT SYMPTOMS IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

R.T. VRABIE[1], A.G. VRABIE[1], M.C. DUGAN-OPAIȚ[2], I.A. BĂDĂRĂU[1], I.R. PAPACOCEA[1]

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] "Pompei Samarian" County Emergency Hospital, Călărași, Romania

INTRODUCTION. *The novel sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initial discovered in Wuhan, China in 2019, and since 2020 it had a major impact on medical practice. Since its discovery it has spread throughout the entire world and the coronavirus disease (COVID-19) was declared a pandemic by the World Health Organization (WHO). At the beginning it was believed that is only a pneumonia with flu like symptoms, but as new cases emerged other symptoms appeared among COVID-19 patients affecting cardiovascular system, gastrointestinal tract and kidney. The interaction between ACE receptors and virus was supposed to be the cause of the various symptoms.*

OBJECTIVES. *The aim of the study was to see the effect of SARS-CoV-2 infection on patients with benign prostate hyperplasia (BPH), between acute infection and after 1 month regarding urological symptoms and to find predictors for urine retention in such patients.*

MATERIALS AND METHODS. *We evaluated all male patients admitted in our hospital with SARS-CoV-2 infection who expressed different forms of COVID -19. We enrolled patients who were previously diagnosed with BPH. We gathered information of their condition prior to infection as prostate volume, postvoiding residual urine, International Prostate Symptom Score (IPSS) and other comorbidities. All enrolled patients were assessed using clinical examination digital rectum examination (DRE), pelvi-abdominal ultrasonography for prostate volume and postvoiding residual urine (PVR) and IPSS for lower urinary tract symptoms. We performed a multivariate analysis to detect the correlation between urinary symptoms and scores and COVID-19 disease.*

RESULTS. *Thirty-tree patients, who were prior diagnosed with BPH, were enrolled. The mean age (±SD) was 71.85 ± 9.12. In the pre and post COVID-19 group, the mean IPSS was 11.76 ± 5.28 and 18.97 ± 7.99 (P <.001), PSA was 1.51 ± 0.9 and 2.23 ± 1.43 (P <.001), while PVR was 12.97 ± 15.12 and 32.7 ± 25.44, respectively (P <.001). After SARS-CoV-2 infection 10 (30.3%) patients needed urinary bladder catheterization because of acute urine retention. On bivariate analysis pre and post COVID-19 IPSS, large prostate on digital rectal examination, pre and post COVID-19 PSA values and post-COVID-19 PVR were significantly correlated with acute urinary retention (P = .008, P = .002, P = .004, P = .033, P = .033, and P = .003, respectively). On multivariate analysis only post-COVID-19 IPSS was the independent predictor for acute urine retention (P =.042).*

CONCLUSIONS. *In patients with BHP, LUTS were affected by COVID-19. SARS-CoV-2 infection increases PSA values, PVR and IPSS leading to changes in the treatment of BPH. There was statistically significant difference between pre and post COVID-19 IPSS and PVR, also post- COVID-19 IPSS was an independent predictor for urine retention.*

Keywords: benign prostate hyperplasia, lower urinary tract symptoms, IPSS (international prostate symptom score), COVID-19, urine retention

INTRODUCTION

Lower urinary tract symptoms (LUTS) are a general term that covers a variety of symptoms related to urination. They are categorized by the moment of occurring as storing, urination or after urination [1]. According to National Clinical Centre (UK) the main symptoms in LUTS are so: storage symptoms as increased daytime frequency, nocturia, urgency, urinary incontinence or altered bladder sensation; voiding symptoms as slow or intermittent stream, hesitancy or straining; after urination as feeling of incomplete emptying or post-urination dribble [2]. For measuring the severity of lower urinary tract symptoms the most used tool in urology across the world is the international prostate symptoms score (IPSS) [3]. LUTS are common associated with benign prostatic hyperplasia (BPH) [4].

BPH represents a proliferative process of cellular elements, both stromal and epithelial cells of the prostate gland. The result is an enlarged prostate that can create voiding dysfunction or bladder outlet obstruction [5]. The present of BHP is linked with age. Langan RC observed in autopsy studies that the prevalence of BPH increases with age [6].

The COVID-19 pandemic basically started in December 2019 in Wuhan, Hubei Province, China with the appearance of new, strange, disease that manifested mostly as pneumonia with flu-like symptoms. From the analysis of respiratory samples, a new type of beta coronavirus was discovered by real-time fluorescence polymerase chain reaction (RT-PCR) [7,8]. Short after the its discovery the World Health Organization officially named it Coronavirus Disease (COVID-19) and by March 2020 it was declared a pandemic [9]. Because of the great number of people infected the outbreak became a world wide concern. The pneumonia resulted from SARS-CoV-2 infection was characterized by fast spread with wide pandemic range and major respiratory disfunction. As the spread of COVID-19 continued globally with 115 million cases and 2.5 million deaths by march 2021 (at 1 year after pandemic declaration by WHO) and by october 2023 it reached 697 million cases and a total of 6.9 million deaths [10]. This fact put a lot of pressure on all health systems around the world and represented a great challenge that effected medical and surgical healthcare. All specialties have faced the difficult challenge of treating COVID-19 patients and urology was no exception.

It is known that other organs, beside lungs, are affected during the infection, such as central nervous system, cardiovascular system, gastrointestinal system, liver, and kidney. For the SARS-CoV-2 to enter and infect the host cell it must bind first with angiotensin-converting enzyme 2 (ACE 2). So, for the virus to infect an organ, the organ must have co-expression of ACE 2 and transmembrane serine protease 2(TMPRSS 2) [11-13]. So the main question that emerged was if the virus can affect organs that have co-expression of ACE 2 and TMPRSS 2 such as testes, kidney, and prostate. A couple of reports observed that SARS-CoV-2 infection has been associated with hematuria and lower urinary tract symptoms [14-16].

Management in health
XXVII/2/2023; pp. 11-14

In this study we assessed the impact of COVID-19 disease on the uro-genital tract function by evaluating the presence of LUTS in patients with PBH.

MATERIALS AND METHODS

We evaluated patients that were admitted to our hospital between March 2021 and October 2022. The inclusion criteria were patients who had previously been treated for BPH. We excluded from the study patients with an active urinary system infection, those with history of urethral stenosis, those with neurogenic bladder or those with previous history of pelvic organ surgery or/and radiotherapy.

All patients were diagnosed with COVID-19 based on reverse transcription-polymerase chain reaction (RT-PCR) tests of oropharyngeal swabs obtained as the recommendation of WHO guidelines. We analyzed the medical history of patients. The evaluation of the patients was done using laboratory investigations (RT-PCR tests, complete blood count, coagulation profile, kidney function, urine analysis and culture, C-reactive protein [CRP] and prostatic specific antigen [PSA]), International Prostate Symptom Score (IPSS) and pelvi-abdominal ultrasonography with prostate volume (PV) and PVR estimation. All patients were managed and treated in accordance with the hospitals guidelines regarding that SARS-CoV-2 infection and the severity of the disease was diagnosed based on symptoms, pulmonary lesions and systemic inflammation. The patients were evaluated during hospital stay, at a month and at 3 months.

The statistical analysis was performed using IBM SPSS Statistics 20.0 (SPSS Inc., Chicago, Illinois), with the usage of proper statistical test according to the type of the variables and their distribution (Student *t* tests, Mann-Whitney *U* tests and chi-squared tests). A *P* value of 0.05 or less was considered statistically significant.

RESULTS

There were 33 patients diagnosed with BPH prior to SARS-CoV-2 infection. The mean age (± SD) was 71.85 ± 9.12 years. From the total number of the patients enrolled 18 (54.5%) had mild COVID-19 symptoms and 10 (30.3%) patients were suffering from diabetes at the time of hospitalization. PSA values ranged from 0.9 to 2.14 ng/ml and 12 (36.4%) patients had prostatic calcifications. The prostatic volume (PV) was estimated by ultrasonography and the mean PV was (± SD) 50.33 ±21.03 cm^3. Postvoiding residual urine (PVR) ranged between 2.5 and 18.5 ml and the mean IPSS value was (± SD) 11.76 ± 5.28. Other patient parameters are shown in Table 1.

There was a significant increase in PSA values (mean ± SD 2.23 ± 1.43 during hospital stay) in comparison with PSA values before infection (1.51 ± 0.90; $P < .001$). There was a statistically significant change in IPSS during hospital stay and its value at 1 month (mean ± SD 11.76 ± 5.28 and 18.97 ± 7.99; $P < .001$). Before COVID-19 infection, the PVR values was 12.97±15.12 cm^3 (mean ± SD) and significantly increased to 32.70 ± 25.44 after infection ($P < .001$) (Table 2).

Table 1. Baseline characteristic of the studied patients

Parameters	Total N = 33
Before COVID-19 infection	
Age (mean ± SD)	71.85 ± 9.12
PSA (median, range)	1.1 (0.9 – 2.14)
IPSS (mean ± SD)	11.76 ± 5.28
PV (mean ± SD)	50.33 ± 21.03
PVR (median, range)	9 (2.5 – 18.5)
Prostatic calcifications n(%)	12 (36.4%)
DRE – large prostate n(%)	13 (39.4%)
Diabetes n(%)	10 (30.3%)
BHP medication - Alpha-blockers n(%)	12 (36.4%)
COVID-19 infection	
CRP (median, range)	52 ± 56.7
Mild COVID-19 symptoms n(%)	18 (54.5%)
Hospitalization days (median, range)	9 (6 -15)
After COVID-19 infection	
PSA (median, range)	1.9 (1.14 – 3.25)
IPSS Score (mean ± SD)	18.97 ± 7.99
PV (mean ± SD)	52.33 ± 21.86
PVR (median, range)	20 (15 – 50)
BHP medication - Alpha-blockers n(%)	29 (87.9%)
Acute urinary retention n(%)	10 (30.3%)

Abbreviations: PSA – prostate specific antigen; IPSS – international prostate symptom score; PV – prostate volume; PVR – postvoiding residual urine; DRE – digital rectal examination; COVID-19 – coronavirus disease 2019; BHP – benign prostatic hyperplasia; CRP – C-reactive protein

Table 2. IPSS, PSA and PVR before and after COVID-19

Parameters	Before COVID-19	After COVID-19	*P* value
IPSS (mean ± SD)	11.76 ± 5.28	18.97 ± 7.99	< .001
PSA (mean ± SD)	1.51 ± 0.90	2.23 ± 1.43	< .001
PVR (mean ± SD)	12.97 ± 15.12	32.70 ± 25.44	< .001

Abbreviations: PSA – prostate specific antigen; IPSS – international prostate symptom score; PVR – postvoiding residual urine

Ten patients (30.3%) were catheterized due to acute urine retention after being infected with SARS-CoV-2. However, none of the studied patients had a urethral catheter before COVID-19 infection. On comparative analysis we found out that PSA values, IPSS and PVR before COVID can statistically corelated with acute urinary retention ($P = .007$; $P = .002$ and $P = .012$, respectively). Also, a large prostate on digital rectal examination before COVID-19 can be a cause of acute urinary retention ($P = .001$) (Table 3).

On bivariate analysis, we found that PVR before COVID-19 and prostate volume after COVID-19 was not associated with urine retention post infection ($P = .087$; $P = .068$). But PSA values, IPSS and large prostate on digital rectal examination and after COVID-19 PSA, IPSS, PVR were significantly correlated with urine retention ($P = .033$; $P = .008$; $P = .004$; $P = .033$; $P = .002$ and $P = .003$, respectively). On multivariate analysis only IPSS after COVID-19 was the independent predictor of urine retention after the acute phase of COVID-19 ($P = .042$) (Table 4).

Table 3. Comparative statical analysis on acute urinary retention

Parameters	Overall (N = 33)	Acute urinary retention (N = 10)	NON- Acute urinary retention (N = 23)	*P* value
Before COVID-19 infection				
Age (mean ± SD)	71.85 ± 9.12	75.9 ± 8.46	70.09 ± 9.01	.093
PSA (median, range)	1.1 (0.9 – 2.14)	1.83 (1.16 – 2.97)	1 (0.77 – 1.88)	**.007**
IPSS (mean ± SD)	11.76 ± 5.28	15.9 ± 3.78	9.96 ± 4.85	**.002**
PV (mean ± SD)	50.33 ± 21.03	59.4 ± 25.33	46.39 ± 18.06	.103
PVR (median, range)	9 (2.5 – 18.5)	18.5 (9.25 – 26.25)	7 (0 – 10)	**.012**
Prostatic calcifications n(%)	12 (36.4%)	4 (40%)	8 (34.8%)	.775
DRE – large prostate n(%)	13 (39.4%)	8 (80%)	5 (21.7%)	**.001**
Diabetes n(%)	10 (30.3%)	2 (20%)	8 (34.8%)	.384
BHP medication - Alpha-blockers n(%)	12 (36.4%)	6 (60%)	6 (26.1%)	.065
COVID-19 infection				
CRP (median, range)	52 ± 56.7	84.5 (45 – 118.75)	47 (17 – 115)	.273
Milder-sever COVID-19 symptoms n (%)	15 (45.5%)	6 (60%)	9 (39.1%)	.268
After COVID-19 infection				
PSA (median, range)	1.9 (1.14 – 3.25)	2.7 (1.9 – 4.51)	1.22 (1 – 2.2)	**.010**
IPSS Score (mean ± SD)	18.97 ± 7.99	27.1 ± 5.58	15.43 ± 6.08	**<.001**
PV (mean ± SD)	52.33 ± 21.86	63.4 ± 25.21	47.52 ± 18.84	.054
PVR (median, range)	20 (15 – 50)	57.5 (36.25 – 80)	17 (10 – 25)	**<.001**
BHP medication - Alpha-blockers n(%)	29 (87.9%)	8 (80%)	21 (91.3%)	.378

Abbreviations: PSA – prostate specific antigen; IPSS – international prostate symptom score; PV – prostate volume; PVR – postvoiding residual urine; DRE – digital rectal examination; COVID-19 – coronavirus disease 2019; BHP – benign prostatic hyperplasia; CRP – C-reactive protein

Table 4. Bivariate and multivariate analysis of the predictors of acute urinary retention post COVID-19 infection

	Bivariate analysis			Multivariate analysis		
Parameters	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Before COVID-19 infection						
PSA	2.658	1.079 - 6.546	.033	-	-	-
IPSS	1.291	1.070 – 1.558	.008	-	-	-
PVR	1.047	.993 – 1.104	.087	-	-	-
DRE – large prostate	14.400	2.289 – 90.597	.004	-	-	-
After COVID-19 infection						
PSA	1.856	1.051 – 3.277	.033	-	-	-
IPSS Score	1.322	1.106 – 1.580	.002	1.233	1.007 – 1.509	.042
PV	1.034	.998 – 1.072	.068	-	-	-
PVR	1.069	1.023 – 1.116	.003	1.033	.977 – 1.098	.254

Abbreviations: PSA – prostate specific antigen; IPSS – international prostate symptom score; PV – prostate volume; PVR – postvoiding residual urine; DRE – digital rectal examination; COVID-19 – coronavirus disease 2019

DISCUSSIONS

In our study we aimed to calculate whether there is a significant difference between urological symptoms describe by patients before and after acute phase of COVID-19 disease. Also we tried to identify any predictable factors regarding worsening of LUTS after SARS-CoV-2 infection.

Gender-related mortality in COVID-19 disease is one of the most reported epidemiological data. Studies conducted in various countries revealed that male gender is linked with a higher grade of vulnerability to COVID-19 infections. For this reason, male gender is considered, by some authors, a poor prognostic factor [17]. A review of epidemiological studies which included 59 254 patients from different countries linked male gender and higher mortality rates [18].

One of the most common causes of LUTS in older man is BPH. So as age remain the main factor to develop BPH so the incidence of PBH increases from 8% in fourth decade to over 70% in seventh decade. For the assessment of LUTS there are 2 approved questionaries, IPSS and American Urology Association (AUA) symptom score [19,20].

Osman et all showed that in patients older than 50 years the IPSS score after COVID-19 was significantly higher than the score before the infection [16].

In our study, we identified that lower urinary symptoms are significantly increased after acute COVID-19 infection, as we find that there was significant increase between IPSS score before COVID-19 (mean ± SD 11.76 ± 5.28) and IPSS after COVID-19 (mean ± SD 18.97 ± 7.99; *P* <.001). Also, ten (30.3%) patients were catheterized, after COVID-19 infection, due to acute urinary

Management in health
XXVII/2/2023; pp. 11-14

retention. The patients who needed to be catheterized had statistically significant greater IPSS score after COVID-19 (mean ± SD 27.1 ± 5.58) than those who didn't presented acute urinary retention (mean ± SD 15.43 ± 6.08; $P < .001$).

In our study we observed that patients with acute urinary retention had a higher CRP values, but, still, there was no correlation between CRP values and higher IPSS with more deterioration in LUTS.

CONCLUSIONS

We were able to identify a correlation between the changes in PSA, IPSS, PVR, DRE after COVID-19 infection, in comparison with the values prior to infection, with the risk of acute urinary retention. Moreover, we observed that IPSS after COVID-19 infection is a predictive factor for urinary retention.

Acknowledgement

This article was published with the support granted by the project entitled "Net4SCIENCE: Applied doctoral and postdoctoral research network in the fields of smart specialization Health and Bioeconomy", project code POCU/993/6/13/154722.

References

1. Abrams P, Cardozo L, Fall M, et al. Standardisation sub-committee of the international continence society the standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. J Neurourol Urodyn. 2002;21:167-178.
2. National Clinical Guideline Centre (UK). The Management of Lower Urinary Tract Symptoms in Men [Internet]. London: Royal College of Physicians (UK); 2010. (NICE Clinical Guidelines, No. 97.) Appendix A, Scope. Available from: http://www.ncbi.nlm.nih.gov/books/NBK65067/.
3. Yao MW, Green JSA. How international is the International Prostate Symptom Score? A literature review of validated translations of the IPSS, the most widely used self-administered patient questionnaire for male lower urinary tract symptoms. Low Urin Tract Symptoms. 2022 Mar;14(2):92-101.
4. McNicholas T, Kirby R. Benign prostatic hyperplasia and male lower urinary tract symptoms. J Am Family Phys. 2012;86:359-360.
5. McNeal JG. The prostate gland: morphology and pathobiology. Monogr Urol. 1983;4:3-33.
6. Langan RC. Benign prostatic hyperplasia. J Prim Care. 2019;46:223-232.
7. Huang C, Wang Y, Li X et al (2020) Clinical features of patients with 2019 novel coronavirus in Wuhan, China. Lancet. https://doi. org/10.1016/S0140- 6736(20)30183-5
8. Lu R, Zhao X, Li J et al (2020) Genomic characterization and epidemiology of 2019 novel coronavirus: implications of virus origins and receptor binding. Lancet. https://doi.org/10.1016/S0140- 6736(20)30251-8
9. WHO announces COVID-19 outbreak a pandemic. https://www.euro.who.int/en/health- topics/health-emergencies/coronavirus- covid-19/news/news/2020/3/who- announces-covid-19-outbreak-a-pandemic.
10. https://www.worldometers.info/coronavirus/. Accesed october 2023.
11. Huang C, Wang Y, LiX, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
12. ChaiX,HuL,ZhangY,HanW,LuZ,KeA,etal. Speci c ACE2 expression in cholangiocytes may cause liver damage after 2019- nCoV infection. bioRxiv. 2020..
13. 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;181:271-80.
14. Almeida FJ, Olmos RD, Oliveira DBL, Monteiro CO, Thomazelli LM, Durigon EL, et al. Hematuria associated with SARS-CoV-2 infection in a child. Pediatr Infect Dis J. 2020;39(7):e161.
15. Mumm JN, 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? Eur Urol. 2020;78(4):624-8.
16. Can O, Erkoç M, Ozer M, Karakanli MU, Otunctemur A. The effect of COVID-19 on lower urinary tract symptoms in elderly men. Int J Clin Pract. 2021 Jun;75(6):e14110.
17. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. J Clin Infect Dis. 2020;ciaa270.
18. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. J Clin Med. 2020;9:941.
19. Partin AW, Oesterling JE, Epstein JI, Horton R, Walsh PC. Influence of age and endocrine factors on the volume of benign prostatic hyperplasia. J Urol. 1991;145:405-409.
20. Karavitakis M, Kyriazis I, Omar MI, et al. Management of urinary retention in patients with benign prostatic obstruction: a systematic review and meta-analysis. J Eur Urol. 2019;75:788-798.