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A study of association of cystitis to SARS-CoV-2 infection in a tertiary care health facility

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Abstract: Introduction: Since December 31st, 2019, SARS-CoV-2 infection (COVID-19) has affected individuals in various ways. During this pandemic, a notable increase in patients presenting with symptoms such as frequency, urgency, burning sensation, hematuria, fever with chills, with or without minimal Influenza-like Illness (ILI), who later tested positive for COVID-19, has been observed. Hemorrhagic cystitis is the most common presenting symptom of viral urinary tract infection (UTI), and some COVID-19 survivors have presented with recurrent hemorrhagic cystitis. These observations prompted us to evaluate the risk factors and association of hemorrhagic cystitis with COVID-19 patients.
Methods: A prospective observational study was conducted among patients presenting with symptoms of cystitis in an outpatient department.
Results: Socio-demographic and clinical characteristics, laboratory and radiological findings were collected, compiled, and analyzed using SPSS ver. 17.0. Out of 152 patients with cystitis, 96 had ILI and subsequently tested positive for COVID-19, and 20 had recovered from COVID-19 in the past month. Hematuria was found as the presenting symptom in 90 (59.21%) patients, with 78 (86.67%) testing positive for COVID-19 and 12 (13.33%) testing negative. According to the Droller et al. grading system, 49% had grade 1 severity, and 32% had grade 2 severity. Diabetes was the most significant risk factor associated with hemorrhagic cystitis.
Conclusion: This study clearly demonstrates an increased prevalence of and association with hemorrhagic cystitis in COVID-19 patients in this tertiary care center. Therefore, routine investigations in SARS-CoV-2 infected cases, such as urine cytology, upper tract imaging, and cystoscopy, will aid in the early diagnosis and proactive management of COVID-19-associated cystitis.

Keywords: Academic stress; Perceived stress; Sociodemographic variables; Health risk; Psychological health; Learning abilities; Mental well-being.

1. Introduction

SARS-CoV-2 infection [COVID-19] has affected different people in different ways since December 31, 2019, when Chinese authorities notified the WHO regarding a novel coronavirus. It causes a wide range of symptoms affecting various organs and tissues in the human body. The most common presenting symptoms include fever, dry cough, tiredness, headache, sore throat, shortness of breath or difficulty breathing, muscle aches, and chills. However, some patients also experience symptoms such as loss of taste, gastrointestinal symptoms (including loss of appetite, nausea, vomiting, and diarrhea), conjunctivitis, skin rashes, or discoloration of fingers or toes, etc.

Mumm et al. reported increased urinary frequency in COVID-19 in a small series of hospitalized patients [1]. The most common presenting symptom of viral urinary tract infection (UTI) is hemorrhagic cystitis. Many affected individuals, whether ambulatory or on ventilator support, developed an overlap of COVID-19 and classic urological symptoms like frequency, urgency, burning sensation, hematuria, and fever with chills during this pandemic. Lamb et al. observed elevated levels of pro-inflammatory cytokines in the urine of confirmed COVID-19 patients and postulated that Chronic COVID-19 Associated Cystitis (CAC) may occur

in COVID-19 patients who do not fully recover and have an ongoing chronic inflammatory condition [2]. Guan et al. detected viral RNA in the urine of COVID-19 patients [3] and hypothesized that infection in the tissues of the urinary tract might cause an increase in urinary frequency. Investigations regarding ACE2 receptor distribution across various tissues revealed that ACE2 expression was highest in the lung, intestines, and kidney, but it was also high in 2.4% of urothelial cells, potentially increasing their susceptibility to SARS-CoV-2 infection and subsequent viral cystitis [4]. The SARS-CoV-2 virus may be able to bind to angiotensin-converting enzyme 2 (ACE2) receptors in the urinary system and cause local inflammation [5]. Additionally, it has been postulated that endotheliitis might play a role in COVID-19 patients [6] and contribute to local inflammation in the bladder.

During the COVID-19 pandemic, there was a significant increase in the number of patients presenting with urinary cystitis to our Urology OPD. Some patients presented with urgency, frequency, and hematuria, with or without minimal Influenza-like Illness (ILI), and later tested positive for COVID-19. Additionally, some COVID-19 survivors presented with recurrent hemorrhagic cystitis or developed chronic cystitis. These observations prompted us to conduct this study to evaluate cases presenting with hemorrhagic cystitis in our OPD setting.

1.1. Objectives

1. To calculate the prevalence of cystitis due to SARS-CoV-2 infection in this study setup.
2. To evaluate the risk factors associated with cystitis in the study participants.
3. To determine the association of hemorrhagic cystitis with COVID-19 status.

2. Materials and Methods

This was a prospective observational study conducted from January 2022 to March 2022 (3 months) among patients presenting with symptoms of cystitis in the Urology OPD of MKCGMCH, Berhampur. Prior to enrollment, Institutional Ethics Committee approval and written informed consent were obtained from all study subjects.

2.1. Inclusion Criteria

- Patients presenting with symptoms of cystitis and with a history of SARS-CoV-2 infection (COVID-19) or Influenza-like Illness (ILI).
- Both genders.

2.2. Exclusion Criteria

- Patients unwilling to give written informed consent.
- Patients who are severely ill and require hospitalization.
- Patients on anticoagulants or antiplatelet agents, radiation therapy, or chemotherapy.
- Patients suffering from bladder tumor, urinary stones, glomerulonephritis, systemic lupus erythematosus (SLE), rheumatoid arthritis, or Crohn's disease.
- Patients undergoing chemotherapy or radiotherapy.

Study Tool: A pre-designed case record form was used.
Sampling Technique: Convenience sampling method was used by enrolling all consecutive patients with cystitis fitting the inclusion criteria during the 3-month study period until the final sample size was reached.
Sample Size Calculation: The sample size was calculated using the formula:

$$n = \frac{(Z_{\alpha/2})^2 \times P \times (1 - P)}{e^2}$$

where:

n = desired sample size,
$Z_{\alpha/2}$ = critical value for the desired confidence level (e.g., 1.96 for 95% confidence interval),
P = expected prevalence or based on previous research (e.g., 0.5),
e = margin of error or precision (e.g., 0.1).

Therefore, our calculated sample size is 97. Assuming 10% attrition, we required a sample size of 107.

2.3. Variables Measured

a. Socio-demographic characteristics: gender, age, smoking status, marital status, education, profession/employment, co-morbidities (hypertension, diabetes, hyperthyroidism, chronic obstructive pulmonary disease, asthma, cancer).

b. Clinical:

i. COVID-19 status (+ve/-ve), history of intensive care unit (ICU) admission (yes/no), history of exposure to COVID-19 (yes/no), family members affected (yes/no), medication history.

ii. Type of cystitis.

iii. Severity of haemorrhagic cystitis grading by Droller et al.

c. Laboratory: Urine analysis for pus cells, white blood cells (WBCs), red blood cells (RBCs), and urine culture.

d. Radiological: Ultrasound (USG) or cystoscopy.

2.4. Statistical Method

The socio-demographic characteristics and clinical data of the patients were analyzed using descriptive statistics. Categorical data were presented as frequency and percentage, while continuous data were presented as mean $\pm$ SD. Student's t-test was used for parametric data, and Fisher's exact test was used for categorical data. Binary regression analysis was used to analyze factors associated with haemorrhagic cystitis in COVID-19 patients. A p-value less than 0.05 was considered statistically significant.

3. Results

A total of 152 patients presented with cystitis during the study period (January 2022 - March 2022), of which 96 had Influenza-like Illness (ILI) and subsequently tested positive for COVID-19, and 20 had recovered from COVID-19 during the past month. Among the patients who had recovered from COVID-19, four had a history of ICU admission. All 96 patients who had presented with ILI or tested positive for COVID-19 later on were included for analysis. The mean age of patients suffering from cystitis was 64.18 $\pm$ 9.35 for the COVID+ve group and 65.60 $\pm$ 9.05 for the COVID-ve group. The sociodemographic profile of the enrolled patients showed that the majority were male (83, 86.45%), married, unemployed, smokers, and had other comorbid conditions associated with COVID-associated cystitis (CAC) (Table 1). Ten patients (10.54%) had pre-existing lower urinary tract (LUT) symptoms, and these patients experienced worsening of their symptoms post-COVID-19. Frequency of micturition, urgency, genital or lower abdominal pain, and haematuria were the most common presenting symptoms. Haematuria as a presenting symptom was found in 90 (59.21%) cystitis patients, with 78 (86.67%) testing COVID+ve and 12 (13.33%) COVID-ve (Table 2). Evaluation of the severity of haemorrhagic cystitis using the Droller et al. grading system revealed that 49% had grade 1 severity and 32% had grade 2 severity. Diabetes and hypertension were the most common associated comorbidities in CAC patients, accounting for 56.09% and 26.82% of cases, respectively (Table 3).

3.1. Risk factors associated with cystitiss in the study participants

On univariate analysis of cystitis in study patients showed that H/o exposure to Covid -19, exposureto affected family members, new onset cystitis and diabetes with glycosuria and haematuria were significantly associated with cystitis. However smoking status, comorbidities like hypertension, hyperthyroidism, COPD, Asthma were not significantly associated. Further multivariate analysis Proved that hematuriain COVID-19 affected patients was significantly associated with cystitis [OR2.92, (1.04-8.21, 'p'value0.042] (Table 4).

Table 1. Socio-demographic characteristics of study participants presenting with cystitis

Sr. No.	Covid-19+ve[n=96]	Covid-19–ve[n=56]	'p'value
Age[Mean±SD]	64.18±9.35	65.60±9.05	>0.05
Gender n, [%] MaleFemale	45(46.87) 51(53.15)	20(35.71) 36(64.28)	>0.05
Maritals tatusn,[%] MarriedUnmarried	88(91.67)* 8(8.33)	49(87.50) 7(12.5)	<0.05
Education status n, [%] LiterateIlliterate	51(53.12) 45(46.87)	46(82.14) 10(17.85)	>0.05
Employment status n,[%] EmployedUnemployed	43(44.79) 53(55.20)*	30(53.57) 26(46.42)	<0.05
Smoking status n,[%] Smoker Non-smoker	40(41.66) 56(58.33)	18(32.14) 38(67.85)	>0.05
Co-morbidities n,[%] Present/Absent	82(85.41)* 10(10.41)	36(64.28) 20(35.71)	<0.05

Table 2. Clinical characteristics of study participants presenting with cystitis

Sl. no	Covid-19+ve[n=96]	Covid-19–ve[n=56]	'p'value
H/o exposure to Covid-19n,[%] Yes/No	80(83.33)* 16(16.67)	6(10.71) 50(89.29)	<0.05
Family members affected, n[%] Yes/No	85(88.54)* 11(11.45)	6(10.71) 50(89.29)	<0.05
! On set of Cystitis, n[%] New Worsening of previous infection	86(89.58)* 10(10.41)	25(44.64) 31(55.36)	<0.05
Type of cystitis, n[%] Haemorrhagic Non-haemorrhagic	78(81.25)* 18(18.75)	12(21.43) 44(78.57)	<0.05

Table 3. Type of co-morbidities among patients suffering from Cystitis [n=118]

Sl. no	Co-morbidity	Covid-19 +ve (%),[n=82]	Covid-19 -ve (%),[n=36]	'p'value
1	Hypertension	22[26.82]	15[41.66]	>0.05
2	Diabetes	46[56.09]*	11[30.55]	<0.05
3	Hyperthyroidism	4[4.87]	1[2.77]	>0.05
4	COPD	3[3.65]	2[5.55]	>0.05
5	Asthma	7[8.53]	7[19.44]	>0.05

Table 4. Laboratory evaluation of CAC

URINE FINDINGS	TOTAL[n=152]	Covid-19+ve[n=96]	Covid-19–ve[n=56]	'p' value
Glycosuria	73(48.03%)	46(47.92%)*	27(48.21%)	<0.05
Hematuria	96(63.16%)	78(81.25%)*	18(32.14%)	<0.05
Pyuria	9(5.92%)	6(6.25%)	3(5.36%)	>0.05
Proteinuria	19(3.94%)	12(12.5%)	7(12.5%)	>0.05
pH	6.14±0.72	6.16±0.75	6.02±0.56	>0.05
Specific gravity	1.02±0.02	1.02±0.01	1.02±0.04	>0.05

Table 5. Multivariate analysis of factors associated with CAC in COVID-19 patients

Factor	Odds Ratio(95%C.I)	'P' Value
H/oexposure to Covid-19	0.34(0.09-1.31)	0.19
Family members affected	1.24(0.57-2.71)	0.59
New Onset Cystitis	2.84(0.79-10.15)	0.11
Diabetes	2.12(0.93-4.85)	0.07
Hematuria	2.92(1.04-8.21)	0.04

4. Discussion

The first wave and second wave of the corona pandemic had witnessed acute respiratory distress syndrome with multiple organ dysfunction as an important cause of morbidity and mortality, and the possible involvement of the genitourinary tract was overlooked during that time. Now, a few studies have established the involvement of the urinary tract in COVID-19 cases, with predominantly lower urinary tract symptoms in less than 5% of patients [8–10]. Over time, COVID-19-associated cystitis (CAC) has emerged as a clinical condition comprising frequency, urgency, lower abdominal discomfort, and nocturia after or during COVID-19 infection. This study showed the prevalence of cystitis among COVID-19 patients to be 63.15%. Some studies have reported that patients with COVID-19 develop new onset or exacerbation of baseline urinary symptoms, most notably overactive bladder (OAB) [11,12], which has been referred to as COVID-19-associated cystitis (CAC) [13,14]. Our study findings suggest the development of CAC among elderly patients, corroborating with the study conducted by Can O et al. [15]. Therefore, elderly patients presenting with COVID-19 need to be evaluated for cystitis. Conversely, elderly patients with increased lower urinary tract symptoms should be evaluated for COVID-19. Like any other viral cystitis, novel coronavirus can also lead to bladder hemorrhage producing hematuria and complications like clot retention [16]. Microscopic hematuria was observed in 49% of COVID-19 patients in our study, substantiating the above study. Routine urine analysis can be used to predict the development of Acute Kidney Injury and may be used as a tool for risk stratification of COVID-19 patients, especially in low-resource settings [17]. Recent studies have reported that COVID-19 is found in human and animal urine [18,19]. Conversely, Wang et al. could not confirm the presence of the virus in urine samples of such patients [20]. Urine analysis findings of the present study revealed a high occurrence of hematuria among diabetic and hypertensive patients with COVID-19. These patients presenting with microhematuria further support the hypothesis of SARS-CoV-2-induced viral cystitis infection of urothelial cells.

COVID-19 patients may present with a possible overlap of symptoms of the lower urinary tract and genital system involvement, with or without typical COVID-19 symptoms. Laura E. Lamb et al. hypothesized that Chronic COVID-19 Associated Cystitis may occur in COVID-19 patients who do not fully recover and have a chronic inflammatory condition ongoing along with elevated proinflammatory cytokines in the urine. Clinicians should be aware of this so that, along with the minimization of the risk of transmission to others, CAC patients can be managed appropriately.

5. Conclusion

Our study clearly shows an increased prevalence, as well as an association of hemorrhagic cystitis in CAC among the patients in this tertiary care center. Further thorough evaluation of SARS-CoV-infected cases by performing routine urine cytology, upper tract imaging, and cystoscopy in hospital setups will help clinicians for early diagnosis and proactive management of COVID-associated cystitis. This will also prevent the significant morbidity of hemorrhagic cystitis in the long run. More research, especially systematic reviews/meta-analyses, will help validate our findings regarding the long-term effects of the novel corona virus on the genitourinary tract.

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