The Effect of Covid-19 Severity on Lower Urinary Tract Symptoms Manifestations

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ABSTRACT
Background: The dominant symptoms in the patient with COVID-19 are symptoms of the respiratory organ system such as cough, rhinorrhea, and shortness of breathing. Nonetheless, some reports found involvement of another organ system, including the gastrointestinal system, cardiovascular system, central nervous system, urinary system, such as lower urinary tract symptoms. Hematuria related to infection of COVID-19 virus on adult and kids were reported. Urinary frequency related to infection of the covid-19 virus was also reported. However, the association between covid-19 infection and lower urinary symptoms was still unknown. Objective This study aims to identify the effect of covid-19 infection on lower urinary tract symptoms manifestation on the patient with COVID-19 treated in Field Hospital. Methods: The design of this study is cross-sectional. After inclusion and exclusion criteria, the male and female patients were then asked based on question points from the International Prostate Score and latest condition related covid-19. In addition, we statistically analyzed the association and the effect between these two variables. Results: Six hundred and six COVID-19 confirmed patients were included in this study. The most frequent complaints of lower urinary tract symptoms were frequency. The severity of the covid-19 correlates with the lower urinary tracts symptoms score. Conclusion: The most common lower urinary tract symptoms are frequency, urgency, and nocturia. These lower urinary tract symptoms may increase in severity with the severity of the infection from COVID-19. The severity of COVID-19 has a significant effect on the increase in lower urinary tract symptoms.

Keywords: Severity, Covid-19, IPSS, Lower Urinary Tract Symptoms.

1. BACKGROUND
Coronavirus 2019 disease (COVID-19) caused by SARS-CoV-2 is a new virus found first in Wuhan, China. This disease has infected millions of people and caused a high death toll worldwide and, in 2020, as a pandemic (1). The disease symptoms vary from no symptoms, mild, moderate, severe, and critical symptoms (2). The dominant symptoms of COVID-19 are respiratory symptoms such as cough, rhinorrhea, and shortness of breath. Many reports informed that other organ systems are involved, including the gastrointestinal, cardiovascular, central nervous, and urinary systems, such as lower urinary tract symptoms (3).

A study reported hematuria and white blood cells in the urine patient with COVID-19 caused by unknown reasons. The provisional hypothesis is that there are acute kidney injuries and urinary tract infections (4,5). Another report by Mumm et al. identified an increased urinary frequency with people with COVID-19 with or without acute kidney injury or urinary tract infection history (6). Several methods of collecting specimens from excretions and secretions have been carried out to assess the status of patients infected with COVID-19 or not. There have been reports of SARS-CoV-2 in the urine of patients with COVID-19. However, the presence of SARS-CoV-2 in urine has not always been shown to be associated with lower urinary tract symptoms (7,8). The exact mechanism by which COVID-19 causes lower urinary tract symptoms is unknown, either through direct replication of SARS-CoV-2 in the urinary tract or due to local and systemic inflammation. The severity of the COVID-19 infection on lower urinary tract symptoms is still unclear.
2. OBJECTIVE

The purpose of this study was to determine the effect of the severity of Covid-19 infection on the prevalence of lower urinary tract symptoms in Covid-19 patients who were undergoing treatment at the Field Hospital.

3. MATERIAL AND METHODS

The research design used in this study was cross-sectional to determine the effect of the degree of COVID-19 infection on the incidence of lower urinary tract symptoms in COVID-19 confirm patients undergoing treatment at the Ijen Boulevard Field Hospital in Malang, Indonesia.

The inclusion criteria used in this study were patients with COVID-19 confirmed by RT-PCR and/or by COVID-19 rapid antigen admitted to the hospital in August 2021. The exclusion criteria were patients with urological malignancies, a history of urological surgery, and patients taking drugs that affect urination patterns.

The severity of Covid-19 infection assessed the patients in this study based on the Guidelines for the Covid-19 Infection Management Protocol, divided into 5, namely asymptomatic, mild, moderate, severe, and critical. Lower urinary tract disorders are divided into three major parts: stored, voiding, and post micturition. IPSS score is used in this study. The IPSS score is used as a questionnaire validated in Bahasa and has been widely used in daily practice to assist in diagnosing and evaluating therapy related to lower urinary tract disorders. IPSS consists of 7 questions that assess incomplete emptying, frequency, intermittency, urgency, weak stream, straining. An IPSS scale of 1-7 is categorized as mild, 8-19 is categorized as moderate, 20-35 is categorized as severe.

To get the value of influence the degree of covid-19 infection on the incidence of lower urinary tract symptoms, a comparative statistical test was carried out between the two variables, and then the relationship test, and it was said that the two variables were related if the p-value <0.05. Therefore, a regression test was done to determine how much influence the degree of COVID-19 infection had on the incidence of lower urinary tract symptoms. The statistical test above was carried out using the Statistical Package for Science (SPSS) software.

4. RESULTS

Six hundred and six patients with confirmed COVID-19 were included in this study. All participants are patients with COVID-19 undergoing treatment at the Field Hospital Ijen Boulevard during August 2021. The age of the patients varies from 11 years to 92 years. The most common comorbidities in patients are diabetes mellitus and hypertension. Cough is the most frequently complained clinical manifestation reported.

### Table 1. Clinical data about LUTS in Patients with Covid-19

| Comorbid | No | Yes | P-value |
|----------|----|-----|---------|
| No       | 256| 230 | 0.006   |
| Yes      | 46 | 74  |         |

| Prevalence Based On Lower Urinary Tract Symptoms |
|-----------------------------------------------|
| Jumlah (N/%)                                  |
| Incomplete emptying                           |
| Frequency                                     |
| Intermittency                                 |
| Urgency                                       |
| Weak stream                                   |
| Straining                                     |
| Nocturia                                      |
| Freq. %                                       |
| No symptom                                    |
| Mild                                          |
| Moderate                                      |
| Severe                                        |
| P     | P   | P   | P   |
| mean  |    |    |    |
| 0.000 | 0.000 | 0.000 | 0.000 |

Based on the results of the test table above, it can be identified that the comparison of the gender of the patients in which patients with lower urinary tract symptoms were found more significant in men and those without LUTS were found greater in female patients with a significance value of 0.000 (p<0.05).

Meanwhile, the results of the comparison by age between groups with lower urinary tract symptoms and those who did not show results where patients with lower urinary tract symptoms tended to be greater in patients aged >50 years, while the results are lower in patients <50 years with a significance value of 0.000 (p<0.05). The comparison results by comorbid condition between groups with lower urinary tract symptoms and those who did not show results where patients with lower urinary tract symptoms tend to have more comorbidities. Lower urinary tract symptoms were frequency
with a prevalence of 21%, namely 130 people were the most frequent complaints found.

Based on the results of the correlation analysis in Table 3 above, it can be seen that the degree of Covid-19 with the IPSS Degree \((r = 0.639, p = 0.000)\) has a significant relationship \((p < 0.05)\) with a positive correlation degree direction (because the coefficient of correlation is positive). It can be concluded that the higher the degree of Covid-19 tends to be followed by a high degree of IPSS as well.

The linear regression analysis test also shows the coefficient of determination \((R^2)\), which states the magnitude of the influence of the Covid-19 degree on the IPSS Degree, in the form of proportions, and other factors determine the rest \((1-R^2)\). So it can be concluded that the degree of Covid-19 affects the IPSS Degree up to 40.8%. Meanwhile, 59.2% of the IPSS Diversity is influenced by other factors besides the degree. In line with our study, men and women aged over 50 tended to experience lower urinary tract symptoms with a significant \(p<0.005\). In addition, men aged also experienced a decrease in the number of B cells and T cells more than women. Resulting in the men having a higher mortality. A history of comorbidity at old age is also more likely to have several comorbidities such as diabetes mellitus, hypertension, and malignancy.

In this study, the relationship analysis showed a significant correlation, with \(p = 0.000 \ (p<0.005)\) regarding the degree of positive correlation. The higher the severity of the symptoms of COVID-19 infection, the higher the IPSS score tends to be. Studies on how the severity of COVID-19 infection can manifest in the urinary tract are still uncertain.

In a previous cohort study by Marand et al., in 238 samples of COVID-19 patients, there were no reports of patients experiencing lower urinary tract symptoms, even though after the urine was examined, the samples showed hematuria and white blood cells, and viral RNA in the urine. The mortality rate in patients with hematuria and pyuria is significantly increased. Another study by Y Ling et al. also reported a viral RNA found in the urine of COVID-19 patients even after recovering from respiratory symptoms, so the viral RNA found in the patient's urine does not necessarily cause lower urinary tract symptoms.

Other studies also reported an association between COVID-19 infection and the incidence of hematuria in children and adults. A case series and retrospective study by Mumm et al. in children and adults also said no viral RNA was found in urine samples. However, in 57 patients, seven patients experienced urinary frequency symptoms as one of the symptoms of COVID-19. The data above shows that symptoms like hematuria, pyuria, added with the presence of lower urinary tract symptoms, such as frequency and urgency, can show occurring cystitis in COVID-19 patients. The possible mechanism by how viral cystitis occurs is due to ACE-2 receptors in the epithelial urinary tract. ACE-2 is also an essential receptor for the SARS-CoV-2 spike protein. Studies of ACE-2 expression in various tissues revealed that ACE-2 expression in the bladder was 2.4%.

Furthermore, respiratory symptoms are the most COVID-19 symptoms reported. Respiratory symptoms can occur from sore throat, fever, cough, shortness of breath to respiratory failure. However, non-expiratory symptoms of COVID-19 patients are also reported. Such as gastrointestinal, neuropsychiatric, and urological. A study reported the lower urinary tract symptoms may be one of the early symptoms of COVID-19 infection.

Based on the research in this study, it was found that the prevalence rate of lower urinary tract symptoms in COVID-19 patients was relatively high. Males suffered from lower urinary tract symptoms significantly \((p<0.005)\). This is the same as one of the epidemiological reports on gender-related covid-19. Studies conducted in several countries show that men are more susceptible to COVID-19. Increased age was also found to increase the incidence of lower urinary tract symptoms. In line with our study, men and women aged over 50 tended to experience lower urinary tract symptoms with a significant \(p<0.005\). In addition, men aged also experienced a decrease in the number of B cells and T cells more than women. Resulting in the men having a higher mortality. A history of comorbidity at old age is also more likely to have several comorbidities such as diabetes mellitus, hypertension, and malignancy.
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symptoms is due to the more severe the level of Covid-19 symptoms, the more organs that experience dysfunction due to infection and inflammation. Inflammation causes damage to the bladder mucosa; this damage results in lower urinary tract symptoms because the damaged urothelium can trigger local afferent nerve activation and impair bladder function (20,21).

6. CONCLUSION
The most common lower urinary tract symptoms in patients with COVID-19 are frequency, urgency, and nocturia. These lower urinary tract symptoms have been shown to increase severity with the severity of the infection from COVID-19 itself. The severity of COVID-19 has a significant effect on increasing lower urinary tract symptoms.

Limitation:
The limitations of this study are that this study only uses the IPSS score with high subjectivity, filling the IPSS score only once in each patient, so that the onset of lower urinary tract symptoms at the beginning or end of the covid-19 infection cannot be known. In addition, other factors such as the patient’s condition at that time, other diseases such as acute kidney injury could not be done because of the limited facilities and infrastructure of the field hospital. The research design is used where this method is weak to assess the cause and effect of a disease. It is essential to do further research to determine the molecular mechanism of how lower urinary tract symptoms occur and the prognosis.

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