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# Association between patient with muscle-invasive bladder cancer with the incidence of urinary tract infection in Karawang Regional Hospital: a single center study

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## ABSTRACT

**Background:** Several studies link urinary tract infection (UTI) and bladder cancer. However, the association between bladder cancer muscle invasiveness and the incidence of UTI is not known.
**Objective:** This study aimed to study the association between the occurrence of UTI in bladder cancer and the severity of the bladder cancer, specifically in a patient admitted to Karawang regional hospital, Indonesia.
**Material and Methods:** This is a single-center retrospective case control. Data were obtained through medical records of the patient admitted with bladder cancer in Karawang Regional Hospital from 2019-2021. Diagnosis of Non-muscle invasive Bladder cancer (NMIBC)/Muscle-invasive Bladder Cancer (MIBC) and UTI were all obtained through medical records. Binary logistic regression analysis was used to determine the odds ratio between these variables and the incidence of UTI.
**Result:** A total of 59 samples were obtained. 57.7% were males, and 42.3% were females, with a mean age of 59 years and distributed into two groups, NMIBC/MIBC. There are also no significant gender and age difference between groups. Our data showed no significant association between bladder cancer muscle invasiveness and the incidence of UTI (OR=1.67; 95%CI 0.218-12.7; p=0.622). Subgroup analysis with different gender also yields no significant result.
**Conclusion:** UTI incidence increased in MIBC patients compared to NMIBC, but it is not statistically significant.

**Keywords:** NMIBC, MIBC, UTI, incidence.
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## BACKGROUND

Bladder cancer is the top 10th most common malignancy worldwide, and its incidence is steadily increasing worldwide. Data from Global Cancer Observatory (GLOBOCAN) showed that in 2020 alone, there were 573.278 new cases of bladder cancer, with 212.536 deaths.[1] In GLOBOCAN 2020, Indonesia showed that bladder cancer counts for 2% of total new malignancies cases in Indonesia, with 3,885 new mortality cases.[2] Bladder cancer is more common in men than women, with an incidence of 9.6/100,000 and 2.4/100,000, respectively.[1] Bladder cancer are generally divided into two types, Non-muscle invasive Bladder cancer (NMIBC) and Muscle-invasive Bladder Cancer (MIBC). Approximately 75% of newly diagnosed bladder cancer are NMIBC present with disease confined to the mucosa or submucosa.[3]

Several studies link urinary tract infection (UTI) and bladder cancer. Many studies showed that persistent or recurrent UTIs are associated with bladder cancer risk. Vermeulen et al. showed that recurrent UTIs are associated with an increased risk of bladder cancer in men and women.[4] This was further confirmed in a meta-analysis that showed a similar result.[5] Furthermore, patients with bladder cancer can seek medical attention with LUTS symptoms as a sole presentation, which urinary tract infections might not always cause.[6] Cancer is generally associated with increased infection due to prolonged immunosuppression and catheter use. One of the most common cancer-related infections is urinary tract infections.[7] However, the association between bladder cancer muscle invasiveness and the incidence of UTI after the patient has been diagnosed is not known. Therefore, this study aimed to study the association between the occurrence of UTI in bladder cancer and the severity of the bladder cancer, specifically in a patient admitted to Karawang regional hospital, Indonesia.

## METHODS

### Study Design and Participants

This is a retrospective case-control study where data was obtained through medical records from Karawang regional hospital between 2019-2021. From the medical records, basic demographic data were obtained along with study variables, including tumor grading, the diagnosis of either MIBC or NMIBC and urinalysis data to diagnose UTI. The diagnosis of either muscle-invasive or non-muscle-invasive and grading of the tumor is based on pathology anatomy data provided in the medical record. Muscle invasiveness of bladder cancer is confirmed through

pathology biopsy results from the medical record. The diagnosis of UTI is based on urinalysis data obtained in the medical record and divided into negative and positive categories. The inclusion criteria for this study were patients admitted to Karawang Regional Hospital with the diagnosis of bladder cancer, and full medical records could be obtained. Exclusion criteria were patients with metabolic diseases such as diabetes, patients with a history of prolonged corticosteroid use, patients with renal or bladder stone disease, and patients with concurrent malignancies other than bladder cancer. Data is obtained, documented, and managed into a table in Microsoft Excel for further analysis.

### Statistical Analysis

All statistical analyses were conducted in SPSS software (IBM Statistic SPSS ver 24.0). Data were first categorized into nominal, ordinal, or numeric. Numeric data normality test was conducted. An Independent T-test was used if the data were normally distributed; otherwise, the Mann-Whitney test was used. Pearson chi-square test was used when comparing two categorical data. Binary logistic regression analysis was used to determine each variable's odds ratio (OR) to the incidence of UTI.

## RESULT

Fifty-nine eligible patients are selected, and their medical records are reviewed. Of these, 57.7% were males, and 42.3% were females distributed into two groups based on the muscle invasiveness of their bladder cancer. The patient's ages ranged from 33-80 years old. The mean age of patients in both NMIBC and MIBC is 59 years old, as seen in Table 1. There is also no significant gender distribution difference (p=0.46) and age (p=0.89) between the two groups.

Our data showed that there is no significant association between bladder cancer muscle invasiveness and the incidence of UTI (OR 1.67; 95% Confidence Interval (95%CI 0.218-12.7; p=0.622) (Table 2).

Subgroup analysis based on gender was also conducted to see whether the association between UTI and muscle invasiveness is gender-dependent. For male patients, UTI incidence is almost the same in both groups. No statistically significant difference was observed (OR 0.98; 95% CI 0.08-11.7; p=0.971) (Table 3). For female patients, MIBC groups had a higher percentage of UTI incidence, but this difference is not significant (p=0.25). Due to the zero number of MIBC female patients that had negative UTI diagnoses, the odds ratio measurement cannot be conducted (Table 4).

**Table 1. Demographics NMIBC and MIBC patients included in the study.**

| | NMIBC | MIBC | p |
|---|---|---|---|
| Age (mean ± SD) | 59.9 ± 10.8 | 59.3 ± 11.9 | 0.89 |
| Gender (n (%)) | | | |
| Male | 31 (56.4) | 3 (75.0) | 0.46 |
| Female | 24 (43.6) | 1 (25.0) | |

**Table 2. Binary logistic regression analysis between muscle invasiveness and incidence of UTI.**

| | UTI negative (n (%)) | UTI Positive (n (%)) | p | OR (95% CI) |
|---|---|---|---|---|
| NMIBC | 35 (62.5) | 21 (37.5) | 0.622 | 1.67 (0.218-12.7) |
| MIBC | 2 (50) | 2 (50) | | |

**Table 3. Subgroup analysis of binary logistic regression for male patients' group.**

| Muscle-invasiveness (male only) | UTI negative (n (%)) | UTI Positive (n (%)) | p | OR (95% CI) |
|---|---|---|---|---|
| NMIBC | 21 (65.6) | 11 (34.4) | | |
| MIBC | 2 (66.7) | 1 (33.3) | 0.971 | 0.98 (0.08-11.7) |

**Table 4. Subgroup analysis of Pearson Chi-square for female patients' group.**

| Muscle-invasiveness (female only) | UTI negative (n (%)) | UTI Positive (n (%)) | p | OR (95% CI) |
|---|---|---|---|---|
| NMIBC | 14 (58.3) | 10 (41.7%) | | |
| MIBC | 0 (0) | 1 (100) | 0.25 | - |

## DISCUSSION

This study is a single-center retrospective case-control experiment that tries to analyze the association between the incidence of urinary tract infection and the severity of bladder cancer. A total of 59 patients are obtained within the period 2019-2021. Only 4 patients (6.7%) in our study are diagnosed with MIBC. An epidemiological study from Global Cancer Observatory (GLOBOCAN) showed that in 2020 there were 573,278 new bladder cancer cases, accounting for 3% of new cancer incidence.[1] In Indonesia, there were 7,828 new cases of bladder cancer in 2020, and this accounted for 2% of the total cancer incidence in Indonesia.[8] Muscle-invasive bladder cancer, however, is rarer than non-muscle-invasive bladder cancer. An epidemiological study showed that MIBC accounts for 20-25% of all newly diagnosed bladder cancer, which is lower in patients younger than 40 years.[9,10] The rarity of MIBC and the sample obtained only from a single center can cause a small number of MIBC patients in this study. In this study, more male patients are admitted with bladder cancer than female patients, with a ratio of 1.36:1. This data matches the epidemiological data but has less gender discrepancy. Data from GLOBOCAN showed that bladder cancer is four times more common in males than females. In 2020 the age-standardized incidence rate of bladder cancer for males and females was 9.5 and 2.4 per 100.000 people, respectively.[11]

Urinary tract infection is the most common cancer-related infection, including bladder cancer.[7] Urinary tract infections in cancer patients are associated with prolonged catheter use and immunosuppressed condition. Many factors might influence local and systemic immune systems in bladder cancer

patients. Malignant and invasive cancer is usually treated with chemotherapy and/or radiotherapy. Guideline from the European Association of Urology (EAU) recommends neoadjuvant cisplatin-based chemotherapy for T2-T4a cN0 M0 invasive bladder cancer in addition to definitive radical cystectomy. EAU guideline also recommends post-operative radiotherapy and neoadjuvant chemotherapy to increase prognosis.[10] The effect of radiation from X-rays and gamma rays can stimulate apoptosis of a cell by causing DNA damage.[12] The effect of ionizing radiation is seen in tumor cells and surrounding tumor microenvironments. Lymphocytes are very radiosensitive cells and can easily be affected by radiotherapy.[13] However, there are no studies linking the effect of lymphocyte destruction due to radiotherapy and the incidence of UTI. The only link between radiotherapy and UTI is seen in a study by Xavier et al., which shows that radiotherapy worsens cystitis, and one patient eventually develops a UTI.[14] Contrary to popular belief that chemotherapy cause immunosuppression in the cancer patient, cisplatin-based chemotherapy has an immunomodulating effect that enhances immune activity in the tumor microenvironment through the stimulation of MHC class I expression, promotes recruitment and proliferation of effector T-cells, and upregulates cytotoxic T-cell antitumor activity.[15-17] Cisplatin-based chemotherapy is also relatively safe and causes less infection.[18] All these factors, therefore, make UTI not a significant symptom associated with muscle-invasive bladder cancer. Thus, this might explain the non-significant association between muscle invasiveness and the incidence of UTI in our data.

To our knowledge, this is the first study to study the association between a higher degree of bladder cancer and UTI incidence after the patient has been diagnosed with bladder cancer. Most of the available literature studies the risk of developing bladder cancer in patients with recurrent chronic UTIs. Vermeulen et al. show that regular low-UTI was associated with increased bladder cancer risk with a stronger effect on muscle-invasive bladder cancer.[4] A systematic review by Anderson-Otunu et al. reports four articles showing a strong association between chronic UTI and bladder cancer and three with weak or no association.[19] A meta-analysis further confirmed by Akhtar et al. showed a significant association between UTI and increased risk for bladder carcinoma both in case-control studies (OR = 2.33; 95% CI 1.86, 2.92) and cohort studies (Relative Risk (RR) = 2.88; 95% CI 1.20, 6.89).[20] Our study shows a different perspective on the relationship between bladder cancer and the incidence of UTI.

There are several limitations to our study. Our data comes from a single center and a regional hospital that does not usually receive many referrals for cancer treatments, making our sample size small. In this study, only four patients were admitted with MIBC in the past two years, from 2019-2021. This small sample size makes statistical analysis doubtful and carries a high risk of false negatives. The second limitation is that this study's retrospective nature makes bias unavoidable. Our study shows an increased percentage of UTI incidence in MIBC patients, but the statistical analysis showed no significant association. With our small sample, this no association is doubtful. Therefore, more research with a bigger sample size and better methodologies (retrospective/prospective cohort studies) are needed to better confirm the relationship between MIBC and increase the incidence of UTI.

## CONCLUSION

Our study reports an increase in UTI incidence in MIBC patients compared to NMIBC, but it is not statistically significant. However, due to the small sample size, our statistical analysis is doubtful and more research with bigger sample size, and better methodologies is needed to confirm this data.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## AVAILABILITY OF DATA AND MATERIAL

Not applicable.

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## CONSENT FOR PUBLICATION

All authors have agreed to publish this paper in the Bali Medical Journal.

## COMPETING INTERESTS

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## AUTHORS' CONTRIBUTIONS

All authors designed the model and the computational framework and analyzed the data, carried out the implementation, performed the calculations, wrote the manuscript with input from all authors, conceived the study and were in charge of the overall direction and planning.

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