# The high prevalence of muscle invasive disease among bladder cancer patients attending a regional hospital in Durban, South Africa

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**Abstract**
**Background:** Muscle invasive bladder cancer (MIBC) comprises 25% of bladder cancers reported in the published literature. It is associated with poor survival, difficult management, and high healthcare costs.
**Objectives:** Our primary objective was to describe the prevalence of MIBC amongst transurethral resection of bladder tumor (TURBT) patients diagnosed with bladder cancer attending a South African regional hospital. Our secondary objective was to describe the characteristics of these MIBC cases.
**Patients and Methods:** We conducted a retrospective chart review of TURBT patients who attended a regional hospital in Durban, South Africa (1 January 2015-31 December 2019). Bladder cancer patients were identified from histopathology reports following TURBT. T-stage classification (T2-T4) was used to identify MIBC cases. We calculated the prevalence of MIBC in bladder cancer patients attending the hospital. Data for patient sociodemographic, clinical, and epidemiological characteristics were also collected and summarized using descriptive statistics.
**Results:** The prevalence of MIBC was 42.7% (44/103 bladder cancer patients). T2 was the most common T-stage in MIBC cases (56.8%). Important features identified in this case series included advanced age, male gender, haematuria, abdominal pain, tobacco smoking, recurrent urinary infection, schistosomiasis, hypertension, bladder mass or hydronephrosis on computed tomography, and palpable bladder mass.
**Conclusions:** The prevalence of MIBC in our study was almost twice that reported elsewhere. Some characteristics reported in our study could be addressed in primary care to reduce MIBC risk or should be investigated for fast-tracking patient referrals to our urology center.
**Keywords:** Urinary Bladder Neoplasms; Bladder Cancer; Muscle Invasive; Transurethral Resection; South Africa.
**DOI**: **10.21608/svuijm.2023.173817.1456**
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**Received**: 26 November,2022.
**Revised**: 27 December, 2022.
**Accepted**: 16 January, 2023.
**Published**: 27 March, 2023
**Cite this article as**: Siphesihle Mbatha, Vishan Mohanlal Ramloutan, Colleen Aldous. (2023). The high prevalence of muscle invasive disease among bladder cancer patients attending a regional hospital in Durban, South Africa. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 2, pp: 68-80.

## Introduction

Bladder cancer is ranked as the 10th most common cancer globally and accounted for 3% of all new cancer diagnoses in 2018 **(Saginala et al., 2020)**. It is amongst the cancers with the highest mortality rates, with 200 000 people succumbing to the disease in 2018 **(Saginala et al., 2020)**. A recent meta-analysis reported that the pooled incidence of bladder cancer in Africa was 7.0 per 100 000 population in men and 1.8 per 100 000 in women **(Adeloye et al., 2019)**. The recent meta-analysis also suggested that the incidence of bladder cancer has been growing in Africa in recent years **(Adeloye et al., 2019)**. This is most likely the result of an increasing burden of risk factors such as tobacco use, occupational exposure to carcinogenic materials or radiation, schistosomiasis, or other emerging risk factors amongst African populations **(Bowa et al., 2018)**.

Common symptoms prompting bladder cancer patients to seek healthcare include haematuria, lower abdominal pain, back pain, urinary tract infection, or urinary retention **(Price et al., 2014; Vermeulen et al., 2015; Holtedahl et al., 2018; Bengtsen et al., 2021)**. In the South African context, a study at a public haematuria clinic in the Western Cape found that patients with bladder cancer comprised 16.4% of the clinic's population **(Sinha et al., 2019)**. In addition to the typical clinical symptoms that have been mentioned, an abdominal mass might also be visible on ultrasound **(Wong et al., 2021)**. Patients with a high index of suspicion for bladder cancer are offered transurethral resection of bladder tumor (TURBT) to remove the bladder mass (if it is safe to do so) and obtain an appropriate specimen of the mass for histopathological diagnosis **(Kim and Patel, 2020)**. Bladder cancer can be sub-classified according to the depth of tumor invasion as non-muscle invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer (MIBC). NMIBC accounts for approximately 75% of bladder cancers reported in the published literature and refers to bladder cancer in which the tumor does not extend into the detrusor muscle (T-staging: Tis, Ta, T1) **(Burger et al., 2013; Hansel et al., 2013; Matulewicz and Steinberg, 2020)**. MIBC accounts for approximately 25% of bladder cancers in the published literature and refers to bladder cancer in which the tumor extends into detrusor muscle (T-staging: T2, T3, T4) **(Burger et al., 2013; Hansel et al., 2013)**. Survival outcomes for patients with MIBC are worse than patients with NMIBC **(Youssef and Lotan, 2011)**. The treatment of MIBC is also far more complex than NMIBC, involving neoadjuvant chemotherapy and radical cystectomy **(Dall'Era et al., 2012)**. Considering the significance of MIBC in terms of its potential impact on patient morbidity, mortality, and expenditure in the South African public healthcare sector, a description of MIBC cases would provide useful information on the magnitude of the disease, common signs and symptoms, and other important characteristics of MIBC in the South African population. This information could lead to better disease control and diagnostic or clinical management of MIBC in South African patients.

The primary objective of our study was to describe the prevalence of MIBC amongst TURBT patients with a diagnosis of bladder cancer attending a South African regional hospital. The secondary

objective of our study was to describe the distribution of important sociodemographic, clinical, and epidemiological characteristics amongst MIBC cases.

## Patients and Methods

### *Study design and setting*

This was a retrospective chart review conducted at a regional hospital, located in the central business district area of Durban, KwaZulu-Natal Province, South Africa. The hospital represents a mid-level facility in the four-tiered referral structure of South African public hospitals. The hospital serves as the urology referral center for most health districts in KwaZulu-Natal Province.

### *Patients*

Retrospective data were collected for consecutive TURBT patients with a diagnosis of bladder cancer who attended the regional hospital from 1 January 2015-31 December 2019. The hospital's theatre records were used to obtain the original list of TURBT patients.

### *Data*

The histopathology report for each TURBT patient with a diagnosis of bladder cancer was reviewed to determine the presence of muscle invasive disease, defined as a tumor biopsy result with a T-stage of T2-T4, as well as tumor grade. The medical records for each of the MIBC cases were reviewed, and data was collected for the following variables – patient sociodemographics, common presenting signs and symptoms, established risk factors, comorbidity, computed tomography findings, urine cytology findings, and examination under anaesthesia findings.

### Statistical analysis

The prevalence of MIBC amongst TURBT patients with a diagnosis of bladder cancer was calculated using the following equation –

$$Prevalence\ of\ MIBC\ (\%) = \frac{\text{Number of patients with MIBC}}{\text{Number of TURBT patients with a diagnosis of bladder cancer}} \text{ X } 100$$

Descriptive statistical analysis was performed using the Statistical Package for the Social Sciences version 27.0 (IBM Corp., USA). The descriptive statistical analyses are presented as frequencies and percentages of all MIBC cases or medians with an interquartile range.

## Results

**(Fig.1)** shows the prevalence of MIBC in our study sample. Of the 112 patients who underwent TURBT at the regional hospital during the study period, 103 had a histological diagnosis of bladder cancer. Of these 103 patients with bladder cancer, there were 44 patients with MIBC (Prevalence of MIBC = 42.7%).

**(Fig.2)** provides a description of T-staging amongst MIBC cases. More than half of all MIBC cases had stage T2 tumor s (n=25, 56.8%), nearly one-third of all MIBC cases had stage T3 tumor s (n=14, 31.8%), and the remainder had stage T4 tumor s (n=5, 11.4%). There were 59 high-grade tumor s (57.3%). Of the 44 MIBC cases, there were 31 cases with transitional cell carcinoma (70.5%), 12 cases with squamous cell carcinoma (27.3%), and 1 case in which the detailed histological findings were not reported (2.2%).

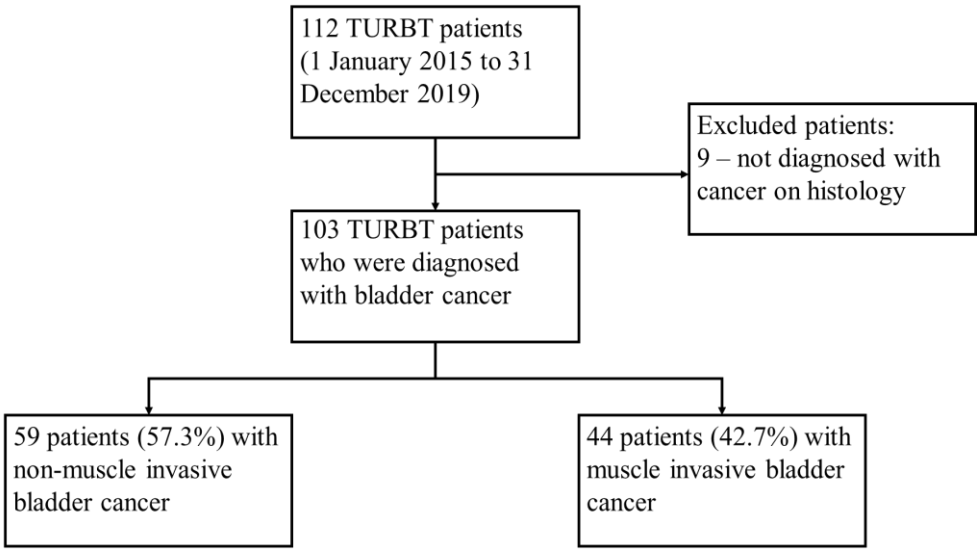


**Fig.1.** Patient flow diagram and prevalence of MIBC in TURBT patients with a diagnosis of bladder cancer

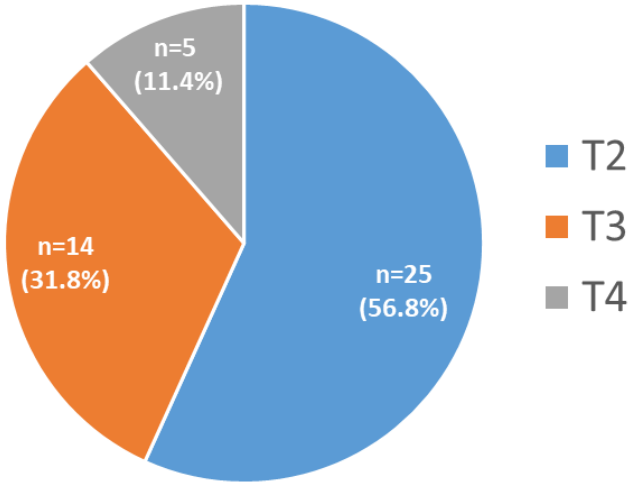


**Fig.2.** T-staging of disease in patients with MIBC

(**Table. 1**) provides a description of important characteristics amongst MIBC cases. The median age was 60.0 years old, and most MIBC cases were male (n= 33, 75.0%). Black Africans were the predominant race group (n=22, 50.0%). The most common signs and symptoms reported were haematuria (n=28, 63.3%) and lower abdominal pain (n=18, 40.9%). Tobacco use (n=19, 43.2%), recurrent urinary tract infection (n=8, 18.2%) and schistosomiasis (n=6, 13.6%) were the most important established risk factors. The most common comorbid condition in MIBC cases was hypertension (n=14, 31.8%). Bladder masses were noted on computed tomography for most MIBC cases (n= 38, 86.4%), while hydronephrosis was noted for almost half of all MIBC cases (n=20, 45.5%). Urine cytology was inconclusive in nearly all MIBC cases (n=43, 97.7%). Most patients with a palpable mass on bimanual examination under anesthesia had a mobile mass (n=30, 68.2%), and nearly one-quarter had a fixed bladder mass (n=10,

22.7%). A total of 27 patients (61.3%) received treatment. Of these 27 patients, there were 16 patients (59.3%) who underwent radical cystectomy and 11 patients (40.7%) who received oncology treatment. Of the 16 patients who underwent radical cystectomy, 10 patients had T2 disease (62.5%) and the other 6 patients had T3 disease (37.5%). Of the 11 patients who had oncology treatment, 8 patients had T2 disease (72.7%), 2 patients had T3 disease (18.2%), and 1 patient had T4 disease (9.1%).

**Table .1.** Descriptive summary of selected characteristics amongst patients with MIBC

| **Patient characteristic** | **n (%) or median (interquartile range)** |
|---|---|
| ***Sociodemographics*** | |
| • Age in years | 60.0 (52.3-66.0) |
| • Male gender | 33 (75.0) |
| • Race - Black African | 22 (50.0) |
| • Race - Indian | 13 (29.5) |
| • Race - White | 7 (16.0) |
| • Race – Mixed | 2 (4.5) |
| ***Signs and Symptoms*** | |
| • Haematuria | 28 (63.6) |
| • Painful micturition | 13 (29.5) |
| • Necroturia | 13 (29.5) |
| • Abdominal mass on ultrasound | 8 (18.2) |
| • Lower abdominal pain | 18 (40.9) |
| • Urinary tract infection | 9 (20.5) |
| • Urinary retention | 3 (6.8) |
| • Back pain | 2 (4.5) |
| ***Risk factors*** | |
| • Tobacco smoking | 19 (43.2) |
| • Industrial work | 1 (2.3) |
| • Schistosomiasis | 6 (13.6) |
| • Family history of bladder cancer | 0 (0.0) |
| • Radiation exposure | 1 (2.3) |
| • Chronic catheterization | 0 (0.0) |
| • Recurrent urinary tract infection | 8 (18.2) |
| ***Comorbidity*** | |
| • Diabetes | 0 (0.0) |
| • Hypertension | 14 (31.8) |
| • HIV infection | 9 (20.5) |
| • Abnormal renal function | 10 (22.7) |
| ***Computed tomography findings*** | |
| • Bladder mass | 38 (86.4) |
| • Hydronephrosis | 20 (45.5) |
| ***Urine cytology findings*** | |
| • High grade urinary carcinoma | 1 (2.3) |
| • Low grade urinary carcinoma | 0 (0.0) |
| • Atypical urinary carcinoma | 0 (0.0) |
| • No malignant cells noted | 0 (0.0) |

| *Bimanual examination under anaesthesia* | |
|---|---|
| Palpable mass - mobile | 30 (68.2) |
| Palpable mass - fixed | 10 (22.7) |
| No palpable mass or inconclusive | 4 (9.1) |

## Discussion

MIBC comprised almost half of all bladder cancers diagnosed in our study. Furthermore, over half of our study's MIBC cases were staged as T2 disease. We also identified several important characteristics amongst South African patients with MIBC, which included advanced age, male gender, haematuria, abdominal pain, tobacco smoking, recurrent urinary infection, schistosomiasis, hypertension, bladder mass or hydronephrosis on computed tomography, and palpable bladder mass.

The prevalence of MIBC amongst bladder cancer patients in our study is almost twice that reported in the published literature - 42.7% in our study versus 25% in the published literature **(Burger et al., 2013)**. It is worth noting that most of the published literature on bladder cancer originates from high-income countries in Europe or North America, which have very different population profiles and risk factor burdens for MIBC when compared to resource-limited African countries **(Chavan et al., 2014)**. These differences might account for the higher prevalence of MIBC amongst our South African sample of bladder cancer patients when compared with populations in high-income countries. More specifically, the impact of globalization on the African populace has been detrimental with regard to health and well-being. There has been increased non-communicable disease risk factors in many African countries over the past few decades as more Africans adopt Western lifestyles. This includes tobacco use, unhealthy diets, and diseases of lifestyle such as hypertension which are risk factors for bladder cancer. Furthermore, there is still persistence of some bladder cancer risk factors in Africa, such as schistosomiasis, which are not very common or have been eradicated in more developed regions of the world. Socioeconomic conditions and resource availability are also very important barriers to early diagnosis and timely treatment of bladder cancer in Africa. Patients might present late for diagnosis of bladder cancer when the disease has spread to the deeper muscle layers. This delay might be due to two main reasons which are commonly encountered in Africa – patients do not access diagnostic services at an earlier stage due lack of transportation to a diagnostic centre/hospital, or because there is limited access to diagnostic laboratories and qualified pathologists in many African countries. Such problems are rarely encountered in more developed countries in Europe and North America. Public health campaigns for urologic cancers, which aim to disseminate information about these cancers and their risk factors, could potentially assist in reducing this wide gap in MIBC burden between resource-limited and high-income countries **(Gapstur et al., 2018)**. Increasing access to urologic cancer screening and encouraging the use of this service for individuals deemed to be at high risk for the disease might also result in early diagnosis of bladder cancer

**(Fradet, 2009)**, which can be treated before progression to MIBC occurs. An analysis of data from a Japanese population of bladder cancer patients undergoing radical cystectomy found that T2 disease was associated with significantly improved overall 5-year survival compared to T3 or T4 disease **(Takahashi et al., 2004)**. Therefore, our finding that just over half of the MIBC cases were staged as T2 disease is encouraging in that it suggests a large proportion of our patients with MIBC are likely to have a good 5-year survival outcome with the current standard of care treatment.

We found older age and male gender to be the most important sociodemographic characteristics amongst MIBC cases. Older age is a well-known risk factor for bladder cancer, as older age is associated with a longer duration of exposure to bladder cancer risk factors **(Shariat et al., 2010)**. However, the median age of patients in our study is much younger than that generally reported for most urologic cancers in a high-income country such as the USA **(Lynch and Cohen, 1995)**, and is more aligned with the age distribution (mean age 58.3 years) reported in an Egyptian study **(Zarzour et al., 2008)**. This suggests an age disparity in bladder cancer between resource-limited and high-income countries which requires further investigation. The preponderance of males amongst MIBC cases in our study confirms the findings from a recent meta-analysis which reported a much higher incidence of bladder cancer amongst males in Africa when compared with their female counterparts **(Adeloye et al., 2019)**. A possible explanation for this finding is that the burden of bladder cancer risk factors might be higher in males than females **(Shariat et al., 2010)**. There might also be underlying differences in the metabolism of carcinogens and sex steroid hormone pathways amongst males and females which explain the difference in bladder cancer burden between the two genders **(Dobruch et al., 2016)**. Although we found that the largest proportion of patients in our study were black African, we suspect that this finding is due to the demographic profile of KwaZulu-Natal Province.

Haematuria and abdominal pain were the most common presenting signs and symptoms amongst MIBC cases in our study. Haemorrhage is part of the natural history of bladder cancer disease **(Fantony and Inman, 2014)**. Accordingly, haematuria is one of the key presenting symptoms of bladder cancer **(Fantony and Inman, 2014)**. Haematuria, particularly macroscopic haematuria, is the most powerful predictor of bladder cancer in primary care settings, with a positive predictive value of 3.9% **(Shephard et al., 2012)**. Thus, haematuria might be useful as a simple screening tool for MIBC in Africa, where access to laboratory services and sophisticated screening equipment is limited. A British primary care study reported that 7% of bladder cancer patients present with abdominal pain **(Shephard et al., 2012)**. The same study found that abdominal pain at presentation was associated with a two-fold higher likelihood of bladder cancer when compared with no abdominal pain at presentation **(Shephard et al., 2012)**. While the prevalence of abdominal pain in our study is higher than that reported in the British study, this is likely because our study sample is restricted to MIBC cases

only. In contrast, the British study included all bladder cancer patients in their analysis, irrespective of the depth of tumor invasion. Despite this, there also appears to be a potential role for abdominal pain, along with macroscopic haematuria, as part of a screening strategy to detect bladder cancer at a much earlier stage in resource-limited health systems.

Tobacco smoking, recurrent urinary infection, and schistosomiasis were the most common risk factors in patients with MIBC. The European Association of Urology cites tobacco use as the most important risk factor for bladder cancer **(Witjes et al., 2021)**. A harmful association between tobacco use and MIBC also exists outside of high-income European countries, with an Egyptian study reporting a 5-fold higher risk of MIBC amongst smokers when compared with non-smokers **(Zarzour et al., 2008)**. The underlying mechanism by which smoking causes bladder cancer is unclear. However, it has been postulated that smoking negatively impacts the p53 gene, which controls the tumor suppressor pathway, giving rise to neoplastic changes in the bladder **(LaRue et al., 2000)**. Our findings confirm the need for smoking cessation interventions amongst populations at high risk for bladder cancer, in keeping with the guidelines for MIBC that the European Association of Urology has published **(Witjes et al., 2021)**. Data from Nijmegen Bladder Cancer Study has demonstrated a positive association between regular urinary infection and bladder cancer **(Vermeulen et al., 2015)**. In the same analysis, the authors reported a risk reduction for bladder cancer in patients with fewer episodes of recurrent urinary infection that were successfully treated with antibiotics **(Vermeulen et al., 2015)**. They also propose that chronic inflammation is the most likely mechanism by which recurrent urinary infection causes bladder cancer **(Vermeulen et al., 2015)**. Studies from Denmark and Taiwan also reported a similar overall association between recurrent urinary infection and a higher risk of bladder cancer risk **(Huang et al., 2019; Pottegård et al., 2020)**. Based on the proportion of MIBC cases with recurrent urinary infection in our study, it appears that more effective antibiotic management of urinary infections at the primary care level is warranted. Schistosomiasis is thought to cause bladder cancer through an inflammatory mechanism **(Nesi et al., 2015)**. Although it is not amongst the main bladder cancer risk factors reported in high-income countries, it remains one of the most important risk factors for bladder cancer in Africa **(Heyns and van der Merwe, 2008)**. It is unsurprising that we have found schistosomiasis to be one of the most frequently reported bladder cancer risk factors in MIBC cases. A study of MIBC in Upper Egypt reported that the risk of bladder cancer was almost 6-fold higher in individuals with a history of schistosomiasis when compared with individuals who did not have a history of schistosomiasis **(Zarzour et al., 2008)**. Therefore, increasing access to safe, clean water supplies in Africa would lead to reductions in communicable diseases and some non-communicable diseases, such as bladder cancer.

The high proportion of patients with hypertension in our study confirms this comorbidity as an important risk factor for bladder cancer. An analysis of data from almost 80 000 patients from

Taiwan reported that patients with hypertension were at a 32% higher risk of developing bladder cancer when compared with non-hypertensive patients **(Kok et al., 2018)**. Furthermore, an analysis of 340 000 Swedish men reported that systolic blood pressure was positively associated with MIBC among never-smokers **(Teleka et al., 2021)**. However, this association was found to be weaker when smokers were included in the analysis **(Teleka et al., 2021)**. The association between hypertension and bladder cancer risk is thought to be related to certain antihypertensive medications **(Xie et al., 2020)**. More studies may be needed to assist in identifying these causative anti-hypertensive medications, and a stepped approach to hypertension management might be appropriate once these medications have been identified.

Urine cytology did not yield conclusive findings for most of the MIBC cases comprising our study sample. The sensitivity of urine cytology for bladder cancer reported in the published literature varies widely (12-85%) and is influenced by factors such as tumor grade, inter-observer variability, urine specimen collection, and urine specimen handling **(Tan et al., 2019)**. It is possible that one or a combination of the above factors, some of which were not measured in our retrospective study, might explain the low diagnostic yield of urine cytology observed in our study. This hypothesis requires further investigation. A bladder mass on computed tomography or a palpable mass when the patient is examined under anaesthesia indicates that the bladder tumor has increased to a large size. This is to be expected in tumor s that are staged T2 or higher and is a potential marker of worse oncologic outcomes when compared with tumor s staged <T2 or smaller in size **(Su et al., 2016)**. Larger tumor size is linked to male gender and smoking **(Su et al., 2016)**, both of which were common characteristics in our MIBC cases. Hydronephrosis on computed tomography was another common finding amongst MIBC cases in our study. Hydronephrosis is considered a strong predictor of upper-tract urothelial carcinoma **(Messer et al., 2013)**. This is because larger, more advanced urothelial cancers cause delayed renal excretion **(Messer et al., 2013)**. A fixed bladder mass is also considered a marker of advanced disease stage in bladder cancer **(Sharma et al., 2009)**, with a large US study reporting the prevalence of fixed bladder amongst patients with bladder cancer at 4% **(Prout et al., 2005)**. Our study reports a much higher prevalence of fixed bladder, but this might be due to our study population consisting solely of MIBC cases rather than a mixture of both MIBC and NMIBC cases as did the US study **(Prout et al., 2005)**. Therefore, the observed proportion of MIBC patients in our study with hydronephrosis and fixed bladder masses is also to be expected, given the advanced disease stage of these patients. Overall, computed tomography and examination under anaesthesia findings might be potential mechanisms that lower-level healthcare facilities can use to fast-track MIBC cases to our urology centre for radical cystectomy. This is very important as delays in radical cystectomy are associated with poor survival outcomes in patients with MIBC **(Chu et al., 2019)**.

Our study has several limitations that must be addressed in future research.

Our study was limited by the fact that we analysed data from a South African public-sector hospital, and our findings might not be entirely applicable to bladder cancer patients who sought care at private hospitals. We do not report on long-term outcomes in MIBC patients due to the high "loss to follow-up" rate in our setting. The retrospective design of our study also limited our analysis to variables routinely collected at the patient's urology clinic visits and during hospital admission for their TURBT. The retrospective study design can also be problematic with missing data in the patient medical chart, and therefore we could not reliably analyse data for some presenting symptoms such as clot retention, frequency of diurnal micturition, and nocturia as information for these symptoms was not consistently collected during the routine medical examinations using a standard format in the patient medical notes. Lastly, some of the risk factor data were based on the patient's self-report and might be susceptible to recall bias.

## Conclusion

The prevalence of muscle-invasive disease in our population of South African bladder cancer patients was almost twice that reported in the published literature from high-income settings, highlighting the need for stronger primary and secondary prevention interventions for bladder cancer in our setting. Some of the common sociodemographic, clinical, and epidemiological characteristics of MIBC cases are potentially modifiable in primary care settings, which could impact reducing the burden of MIBC. On the other hand, we have identified several characteristics that we feel should be investigated at lower-level facilities to fast-track MIBC cases for radical cystectomy at our urology center.

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