

## Prevalence, Etiology and Characteristics of Urethral Stricture at a National Referral Hospital in Tanzania

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**Abstract**

**Background:** Urethral stricture results from urethral fibrosis leading to bladder outlet obstruction. The most common signs include reduced urinary volume, urgency, dysuria, incontinence, lower abdominal pain, urethral discharge, blood in the semen and/or urine and recurrent urinary tract infections (UTI) due to post void residue. It imposes a great burden on the quality of life in men. There is paucity of literature in Tanzania on urethral stricture, therefore this study aimed to determine its prevalence, causes and characteristics in terms of the commonest site affected, the management options used and the most common complications occurring in the patients for a period of five years in order to have an insight on the pattern of the disease over the years.

**Broad Objective:** To determine the prevalence of operated urethral stricture disease, its etiology and characteristics including the commonest site affected, commonest investigation and treatment options used as well as the most common complications developed at Muhimbili National Hospital (MNH) from the year 2012 to 2016.

**Methodology:** A descriptive retrospective cross-sectional study was conducted at MNH whereby all the patients operated for urethral stricture from 2012 to 2016 were included. Data was collected from the files of the patients at the medical records after obtaining an ethical clearance. Data was analyzed by Statistical Package for Social Sciences version 20. Data were presented by using tables and histograms which showed the prevalence of urethral strictures operated at MNH from 2012 to 2016, the most common causes, the commonest location, the commonest complications seen, the most frequent investigations as well as the surgical treatment options used. The results enable us to see the pattern and the findings from one year to another.

**Result:** A total of 4170 patients were admitted for various urological pathologies from 2012-2016. Among these, 646 (15.5%) were operated for urethral strictures. Out of the 646 urethral stricture cases, only 303 (46.9%) files could be obtained from the records and were included in the study. Majority of the study population were aged 60 years and above. Almost all patients (99.7%) were males. The most common cause of the urethral stricture was seen to alternate between trauma, iatrogenic and infectious cause whereby the cause was seen to change from year to year. Bulbar urethra was the most frequent site affected. Urinary retention was the most common complication over the years except for the first year where UTI was reported to be the highest. Urethrogram was most commonly used for the diagnosis and direct vision internal urethrotomy (DVIU) was most frequently performed for the treatment of urethral stricture in these five years.

**Conclusion:** The prevalence of urethral stricture cases that were operated within the five-year period ranged from 15.1% to 17.3%. It was most commonly seen in the older age group. The cause was seen to be alternating between trauma, iatrogenic injury and infections within the five-year period. Bulbar urethra was the most commonly affected site with urinary retention and recurrent UTI being the commonest complications. Urethrogram was most commonly used for the diagnosis and the commonest surgical procedure done was DVIU.

**Key words:** Pattern, Urethral Stricture, Urethrogram, Direct Vision Internal Urethrotomy.

**Introduction**

The urethra is the channel through which urine is emptied from the bladder. Its length is around 20cm in males, and it is divided into an anterior and posterior segment. The anterior part is composed of the meatus, fossa navicularis, penile (pendulous part) and the bulbar portion. The membranous and prostatic urethra make up the posterior segment (1). The female urethra is approximately 4 cm in length and 6 mm in width. It begins at the internal vesical orifice, extends downwards and forwards behind the symphysis pubis embedded in the anterior vaginal wall and terminates at the external urethral meatus (2).

Fibrosis of the urethra causes urethral stricture and leads to bladder outlet obstruction (3). Signs and symptoms of urethral stricture vary from mild to severe. The most common signs include reduction in the volume of urine, urinary urgency, pain while urinating, urinary incontinence, lower abdominal pain, discharge from the urethra, penile swelling, blood in the semen and/or urine, darkening of the urine and recurrent urinary tract infections due to post void residue. This disease imposes a great burden on the health and quality of life in men.

Urethral strictures lead to complications of the urinary tract. One of the major complications reported is urinary tract infection. Other commonly reported complications include formation of bladder stones, vesicoureteral reflux, urethrocutaneous fistula and hydroureteronephrosis. A long standing disease may impair the renal function eventually causing chronic renal failure (1). Urinary retention, carcinoma of the urethra, Fournier's gangrene and failure of the bladder to contract are among the severe complications that are seen in patients with urethral stricture (4).

The pattern of urethral stricture keeps changing from one year to another. Urinary bladder outlet obstruction caused by urethral stricture accounts for a large number of patients attending the urology unit at Muhimbili National Hospital (MNH). Approximately, 150 urethral strictures are treated per year, yet the pattern of this disease is not well documented (1). Very little is known on the pattern of urethral stricture in Tanzania. Therefore, the aim of this study was to assess the characteristics of urethral stricture disease among patients operated at MNH over a period of five years in order to see if there were any changes in this area in terms of the prevalence of the disease, its causes, most common site affected in the urethra, the management option used, and the complications seen as a result of this disease.

## Methodology

### Study area

This study was conducted at MNH, a public tertiary hospital located in Ilala Municipality (with an estimated area of 273-kilometer square) in Dar es Salaam, Tanzania. MNH is a National Referral Hospital, Research Center and University Teaching Hospital. The mission of this hospital is to provide effective, efficient and high-quality tertiary specialist medical services for referred patients from all over Tanzania, while providing conducive environment for training and research. It receives referral cases from the Eastern zone and other parts of Tanzania with 1500 bed facility and particularly the surgical ward has a total of 220 beds in which 62 beds are for the urology unit. The department that deals with the cases of urethral stricture is the surgery department under the urology unit and the study was specifically based in this unit.

### Study design

This was a hospital based descriptive retrospective cross-sectional study that included patients operated for urethral stricture at MNH from 2012 to 2016.

### Sample size calculation

The minimum sample size of the study participants was calculated by using the Kish and Leslie formula for determination of proportion in cross sectional studies as shown below:

The sample size was calculated from the formula: 
$$n = \frac{Z^2 P(100-P)}{\epsilon^2}$$

n= estimated sample size

Z= percentage point of the normal distribution corresponding to the level of significance <5%, Z= 1.96

P= proportion of patients with urethral stricture detected using contrast retrograde X-ray urethrogram in black Africans = 84.6 % (11)

ε= margin of error, which is approximately 5%

$$n = \frac{(1.96)^2 \times (84.6) \times (100-84.6)}{5^2}$$

n= 200

### Sampling technique

A consecutive sampling technique was used whereby all available files of patients operated for urethral stricture and operated during the study period were included in the study. The files were obtained from the medical records of MNH which stores the details of all the

patients treated at MNH. The file numbers were obtained from the register books at the theatre for all the patients operated on within these five years and then the files of those patients were provided by the medical records department.

## Study Population

The study involved all patients who had been operated for urethral stricture at MNH from 2012 to 2016.

## Inclusion criteria

All patients operated for urethral stricture within the period of study were included irrespective of their age and sex.

## Data collection

The file numbers of patients with urethral stricture were obtained from the register books at the theatre for all the patients operated within the five years from 2012 to 2016 and then the files of those patients were provided by the medical records department. There was a structured checklist with two sections for the data collection process, the first one being the demographic data and the second one being the clinical data. The demographic data of the patient was taken from the file which included the sex of the patient, the age, the occupation, the marital status and the education level. The clinical data obtained from the clinical history noted down in the file gave the cause of the stricture and the complications that the patients developed as a result of the urethral stricture were also noted. The radiological findings in the file gave the site of the stricture and the information from the operating procedures gave the mode of treatment that was offered to the patient. For each of the objectives, the patients with some missing data were grouped separately and that category was labelled as not documented.

## Data analysis

Data was fed into Statistical Package for Social Sciences (SPSS version 20) and was analyzed by using the same software. The data was summarized by using tables and histograms which showed the prevalence of urethral strictures operated at MNH from 2012 to 2016, the most common cause, the commonest location, the commonest complication occurring as a result of the urethral stricture and the most frequent investigation used for the diagnosis as well as the surgical treatment option used for the urethral strictures operated at

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MNH. Data obtained from each of the five years was used to compare the findings from one year to another and see the pattern of the disease over the period of these five years.

### Ethical clearance and consideration

The ethical approval to conduct this study was obtained from Muhimbili University of Health and Allied Sciences (MUHAS) Research and Ethics Committee. Permission to conduct the study at MNH was obtained as per the MNH guidelines for conducting research. Confidentiality and privacy were observed towards the patients' information whereby names of the patients were not included as part of the checklist. The checklist with the patient's information was handled with care to ensure confidentiality. The checklist was disposed of carefully in an ethical way by burning them so as to protect the information.

### Results

A total of 4170 patients were admitted for various urological conditions from 2012-2016. Among these, 646 (15.5%) were urethral strictures. Out of these 646 urethral stricture cases, only 303 (46.9%) files could be obtained from the records as the other files were missing and thus information about those patients could not be obtained. Among these 303 patients, 302 (99.7%) were males and only 1 (0.3%) was a female. Therefore, the rest of the analysis will involve 303 patients' information as the representative of the study population. The prevalence of urethral stricture was found to be 15.5% from the year 2012 to 2016 (Table 1).

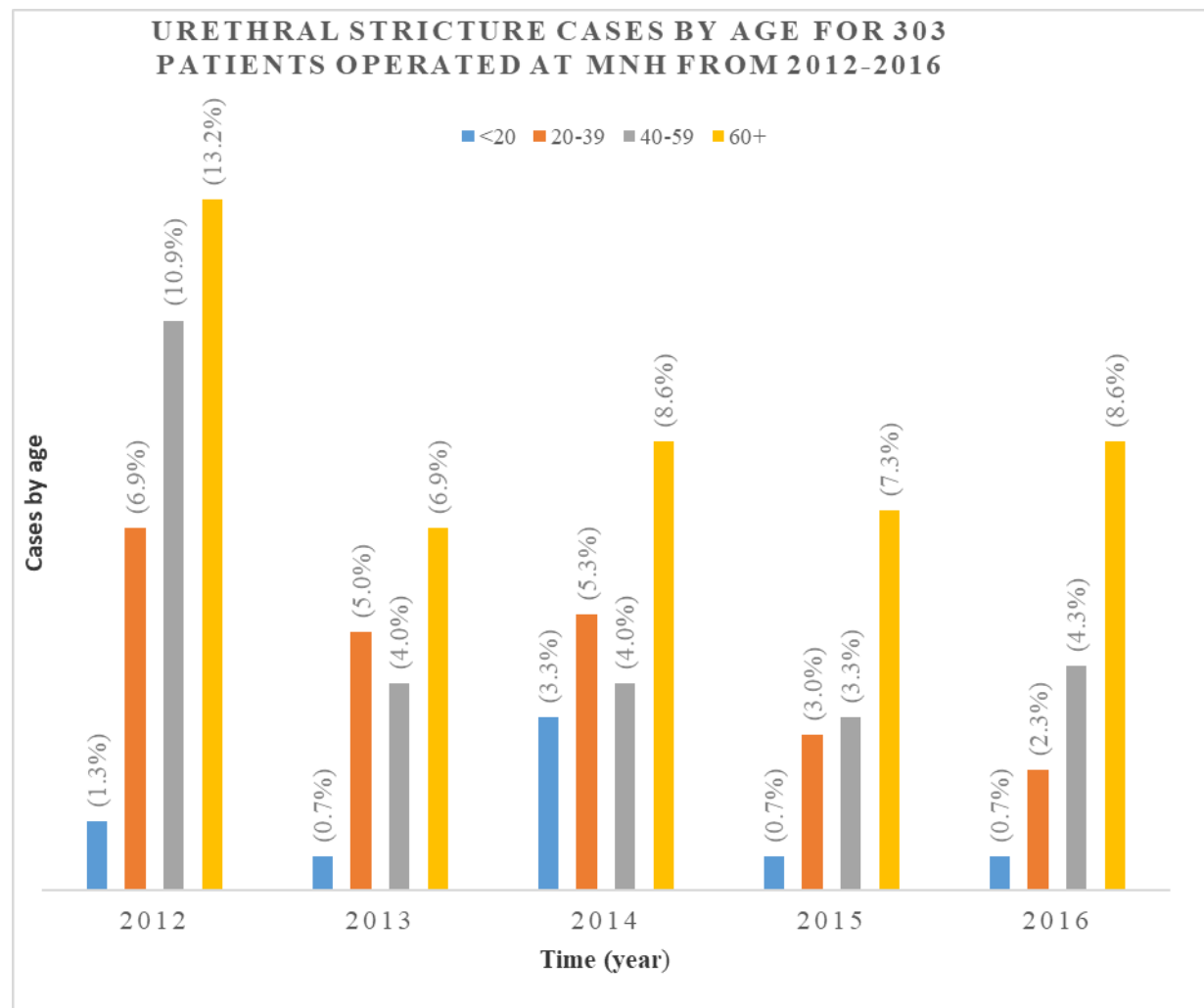
**Table 1: Proportion of urethral stricture over other urological cases by year from 2012-2016**

Year	Urethral Stricture (N)	Other Urological Cases (N)	Total Number of Urological Cases (N)	Proportion Of Urethral Stricture (%)
2012	157	753	910	17.3
2013	103	578	681	15.1
2014	139	721	860	16.2
2015	149	823	972	15.3
2016	98	649	747	13.1
<b>Total</b>	<b>646</b>	<b>3524</b>	<b>4170</b>	<b>15.5</b>

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The number of cases of urethral stricture was found to increase with increasing age as shown in the histogram below; whereby in each year, the largest proportion of patients were constituted by those aged 60 years and above (Figure 1).



**Figure 1. Urethral stricture cases by age groups among 303 patients operated at MNH for each year from 2012 to 2016**

Throughout the five-year period, the cause of urethral stricture was not documented for some patients, with the highest being in 2016 (77.1%). The leading cause of the stricture has been changing over the years whereby infection was reported to be the most common cause in 2012 (22.4%) and in 2015 (18.6%). Iatrogenic injury was the highly reported in 2013 (36%) and in 2016 (12.5%). In 2014, trauma was the leading cause of urethral stricture (26.6%) (Table 2).

**Table 2: Causes of urethral stricture in patients operated for urethral stricture at MNH from 2012-2016.**

Causes of Urethral Stricture	Years				
	2012	2013	2014	2015	2016
	Frequency				
Trauma	N (%)	N (%)	N (%)	N (%)	N (%)
Road traffic accident	12	5	12	3	1
Falling astraddle on metal or hard objects	3	2	4	1	0
Direct external violence	0	0	1	0	1
<b>Total</b>	<b>15 (15.3%)</b>	<b>7 (14.0%)</b>	<b>17 (26.6%)</b>	<b>4 (9.3%)</b>	<b>2 (4.2%)</b>
<b>Iatrogenic</b>					
Urethral catheterization	15	13	8	3	3
TURP	5	5	1	2	3
Urethrocystoscopy	1	0	0	0	0
Circumcision	0	0	1	0	0
<b>Total</b>	<b>21 (21.4%)</b>	<b>18 (36.0%)</b>	<b>10 (15.6%)</b>	<b>5 (11.6%)</b>	<b>6 (12.5%)</b>
Infection	22 (22.4%)	6 (12.0%)	4 (6.3%)	8 (18.6%)	3 (6.25%)
<b>Other causes</b>					
Urethral tumor	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)
Not documented	40 (40.8%)	19 (38.0%)	32 (50.0%)	26 (60.5%)	37 (77.0%)
<b>TOTAL</b>	<b>98 (100.0%)</b>	<b>50 (100.0%)</b>	<b>64 (100.0%)</b>	<b>43 (100.0%)</b>	<b>48 (100.0%)</b>

Bulbar urethra was found to be the most frequent site of stricture over all the period of five years while prostatic urethra was the least affected site. Most of the patients had multiple urethral strictures, meaning that they had more than one stricture at the same site or at different sites in their urethra (Table 3).

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**Table 3: Location and number of urethral strictures in patients operated for urethral stricture at MNH from 2012-2016**

Location/ Number of Urethral Stricture	Year				
	2012	2013	2014	2015	2016
	Frequency				
	N (%)	N (%)	N (%)	N (%)	N (%)
Bulbar urethra	78 (45.9%)	42 (50.0%)	51 (45.9%)	32 (48.5%)	41 (53.2%)
Penile urethra	50 (29.4%)	25 (29.8%)	29 (26.1%)	18 (27.3%)	15 (19.5%)
Membranous urethra	33 (19.4%)	14 (16.7%)	26 (23.4%)	13 (19.7%)	18 (23.4%)
Prostatic urethra	9 (5.3%)	3 (3.6%)	5 (4.5%)	3 (4.5%)	3 (3.9%)
<b>Total</b>	<b>170</b>	<b>84</b>	<b>111</b>	<b>66</b>	<b>77</b>
<b>Number of Strictures</b>					
Multiple strictures	58 (59.2%)	29 (58.0%)	40 (62.5%)	21 (48.8%)	20 (41.7%)
Single stricture	38 (38.8%)	21 (42%)	23 (35.9%)	21 (48.8%)	28 (58.3%)
Location/ Number not documented	2 (2.0%)	0 (0%)	1 (1.6%)	1 (2.3%)	0 (0%)
<b>Total</b>	<b>98</b>	<b>50</b>	<b>64</b>	<b>43</b>	<b>48</b>

It was evident that urinary retention was the most common complication of urethral stricture in all the years except for 2012 where urinary tract infection was reported to be the highest (Table 4).

Urethrogram was the investigation that was mostly used for the diagnosis of urethral strictures compared to other imaging modalities throughout the five-year period. DVIU was the most frequently performed procedure for treatment of urethral stricture in these five years. Multiple procedures as mentioned in the table below refers to more than one procedure performed for the treatment of urethral stricture on a single patient as a result of failure of all the other previous procedures that were done. The total number of patients exceeds 303 due to the fact that more than one investigation was done in a single patient for confirming the diagnosis of urethral stricture and some of them underwent more than one surgical procedure during the course of their illness (Table 5).

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**Table 4: Complications of urethral stricture in patients operated for urethral stricture at MNH from the year 2012 to 2016**

Complications of Urethral Stricture	Year				
	2012	2013	2014	2015	2016
	Frequency				
	N (%)	N (%)	N (%)	N (%)	N (%)
Acute urinary retention	40 (37.0%)	20 (39.2%)	22 (40.0%)	12 (33.3%)	7 (36.8%)
Urinary stasis and UTI	44 (40.7%)	17 (33.3%)	18 (32.7%)	13 (36.1%)	8 (42.1%)
Urethrocutaneous fistula	6 (5.6%)	5 (9.8%)	7 (12.7%)	0 (0.0%)	3 (15.8%)
Hydronephrosis	5 (4.6%)	5 (9.8%)	4 (7.3%)	5 (13.9%)	0 (0.0%)
Bladder stones	6 (5.6%)	1 (2.0%)	2 (3.6%)	1 (2.8%)	1 (5.3%)
Orchitis	5 (4.6%)	1 (2.0%)	1 (1.8%)	2 (5.6%)	0 (0.0%)
Renal failure	0 (0.0%)	2 (3.9%)	0 (0.0%)	2 (5.6%)	0 (0.0%)
Vesicoureteral reflux	2 (1.9%)	0 (0.0%)	1 (1.8%)	1 (2.8%)	0 (0.0%)
<b>Total</b>	<b>108</b>	<b>51</b>	<b>55</b>	<b>36</b>	<b>19</b>

**Table 5: Investigations and surgical procedures done on patients operated for urethral stricture at MNH from the year 2012 to 2016**

Investigations Used	Year				
	2012	2013	2014	2015	2016
	Frequency				
	N (%)	N (%)	N (%)	N (%)	N (%)
Urethrogram	81 (43.8)	41 (46.6)	44 (40.7)	31 (48.4)	24 (36.4)
Urethrocystoscopy	47 (25.4)	24 (27.3)	42 (38.9)	14 (21.9)	22 (33.3)
Ultrasound	57 (30.8)	23 (26.1)	22 (20.4)	19 (29.7)	20 (30.3)
<b>Total</b>	<b>185</b>	<b>88</b>	<b>108</b>	<b>64</b>	<b>66</b>
<b>Surgical Procedure Used</b>					
DVIU	72 (45.9)	35 (50.0)	44 (55.0)	32 (57.1)	35 (63.6)
Single stage urethroplasty	39 (24.8)	21 (30.0)	24 (30.0)	16 (28.6)	14 (25.5)
Multiple procedures	27 (17.2)	12 (17.1)	10 (12.5)	7 (12.5)	5 (9.1)
Dilatation	13 (8.3)	2 (2.9)	2 (2.5)	0 (0.0)	0 (0.0)
Multistage urethroplasty	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Stent	2 (1.3)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
<b>Total</b>	<b>157</b>	<b>70</b>	<b>80</b>	<b>56</b>	<b>55</b>

**Discussion**

In this study, the prevalence of urethral stricture in the five-year period was found to be 15.5%. The number of admissions for urethral strictures requiring surgery was found to be fairly constant within the five-year period ranging from 15.1% to 17.3%. A study done by Amjad Alwaal et al in 2014 revealed that urethral stricture was commonly reported in elderly men with an associated prevalence of 229-627 per 100,000 males or 0.6% of the population at risk (5). Another study conducted by Santucci et al also reported different findings as compared to our study whereby they reported a decrease in the proportion of urethral stricture over the years postulating that this could be due to timely detection and treatment of sexually transmitted infections such as gonorrhea (6). The findings obtained in our study could be due to the fact that the causes of the stricture were not addressed, and no immediate actions were taken to prevent them such as spreading of awareness to the public on the magnitude of this problem and the necessary precautions to be taken, as a result patients presented with the same problem throughout the years of the study.

Urethral stricture was seen to occur most commonly in older men aged 60 years and above with a mean age of 52.47 years. Almost all the patients in the study were males (99.7%) except for one female (0.3%). These results were very similar to a study conducted in 2011 in the same setting by Obadia et al whereby all the patients were males, and the mean age was reported to be 52.7 years (1). These results are also very similar to those reported by another study conducted by Eshiobo in 2017, where the mean age was 53.11 years and all the participants were males (7). The pattern in terms of the age and sex has not changed over the years as in most cases majority are males and belong to the older age group. This can be attributed to the anatomy of the urethra, being longer in males and forms an "S" curve when viewed from a median sagittal plane in an upright, flaccid position predisposing the males to a higher chance of injury. The older men also experience various other urological diseases such as those related to the prostate which requires them to undergo repeated instrumentation to the urethra posing a great risk of developing urethral stricture.

The common cause of the stricture appeared to be varying from one year to another. Infection was reported to be the most common cause in 2012 (22.4%) and in 2015 (18.6%). Trauma was the leading cause of urethral stricture in 2014 (19.1%) in which road traffic accidents were the major culprits causing the rise in urethral stricture cases. In 2013 and 2016, iatrogenic injury was the most common cause reported, represented by 34% and 12.6% of cases, respectively. Urethral catheterization was found to be the most common cause of iatrogenic injuries as compared to other causes throughout the five-year period.

This could be explained by the fact that the diseases related to old age for instance hypertensive stroke necessitates prolonged catheterization and as a result predisposes the patient to a greater risk of developing urethral stricture. In addition to this, elderly men with diseases of the prostate also undergo multiple repeated procedures predisposing them to stricture formation. Other reasons may include inefficiently trained staff, usage of wrong size of catheters, inadequate lubrication, failure of catheterizing aseptically and prolonged catheterization (1). The cause of the stricture has been changing yearly but the study period was not sufficient enough to conclude, a longer duration of study may be required to note the change in the cause of the stricture with time.

The most commonly affected site was the bulbar urethra in each year throughout the five-year period. In the first three years of the study, more than half of the patients had multiple strictures which were as follows; in 2012 (59.2%), in 2013 (58.0%) and in 2014 (62.5%). In the fourth year, there was an equal number of patients with single and multiple strictures, each was represented by 48.8%. In 2016, the final year of the study, majority had a single stricture (58.3%). Similar findings were seen in a study done by Eshiobo in 2017, whereby bulbar urethral stricture was the most common site accounting for 69.6% of the patients (7). This finding can be explained anatomically, and one reason is that the double curve in the bulbar urethra slows down the urine flow in that section due to the presence of the periurethral glands and abundant corpus spongiosum increasing a likelihood of infection to set in. It can also be explained by the fact that the inferior position of the urethra relative to the pubis predisposes it to fall astride crush injury easily causing trauma to the urethra. Our study revealed that the prostatic urethra was the least affected site throughout the study period. A study done by Ekeke in 2016 also revealed similar findings (8). It is evident when comparing the two studies that the pattern in terms of the commonest location affected has not changed over the years. The bulbar urethra has been seen to be the most affected one and the prostatic urethra the least affected location.

The complications of urethral stricture that were common in this study were urinary retention and recurrent urinary tract infection. In 2012, 2015 and 2016 urinary retention was the most reported complication represented by 44.9%, 30.2% and 16.7%, respectively. Urinary tract infection was the most common complication in 2013 (40.0%) and in 2014 (34.4%). Anger et al evaluated Medicare claims to assess the rates of urinary tract infection over a number of years. Urinary tract infection as a complication of urethral stricture was seen to increase from 35% in 1992 to 42% in 2001; this was noticed across all age groups and races analyzed (4). These findings were similar to our study whereby urinary retention and

recurrent urinary tract infection were presented as the commonest complication of urethral stricture. This is a clear indication that the pattern in terms of the complications has not changed over the years whereby majority of the patients present with these complications.

From our study it was evident that urethrogram was the most common investigation used for the diagnosis of urethral stricture in more than half of the patients throughout the study period in all the five years. A study done in India in 2014 comparing the retrograde urethrography, with sonourethrography found that they were both equally effective and equally efficacious in identifying an anterior urethral strictures (10). It was evident that the pattern has not changed in terms of the investigation used as urethrogram has always been the investigation of choice for the diagnosis of urethral stricture over the years. This is mainly because the results are reliable showing the site of the stricture and it is cost effective for the patients as well.

A large number of patients in each of these five years underwent DVIU and this was followed by single stage urethroplasty. A study conducted by Obadia in 2011 at MNH and Tumaini hospital in Dar es Salaam also revealed similar findings whereby DVIU accounted for a large percentage of the treatment offered followed by single stage urethroplasty (1). The surgical treatment given to the patients in this study openly revealed that there was no change in terms of the treatment offered. Patients treated at MNH were mostly subjected to DVIU as the main surgical option. However, when comparing this study to a study done in Nigeria, the differences in the treatment offered in different countries was observed. They used more of dilatation whereas in our setting dilatation was the least preferred method of treatment (3). The reason for DVIU being used commonly may be due to the ease of doing it and hence it is preferred by the surgeon. Nevertheless, it has a high rate of recurrence leading to multiple procedures being done on the patient and thus resulting in poor prognosis.

### **Limitations of the study**

More than half of the files were not available at the records department and those present had incomplete data. The patients whose files were missing were not included in the study, however those with incomplete data were included in the study. The information that was missing or was incomplete was classified in its own category as not documented. A large number of sample size is preferable as it increases the strength of the study. In this study, more information could not be obtained due to missing files. Careful storage of information is urged so as to retain the patients' information for further research.

Another limitation of this study is that it only involves the patients who were operated on for urethral stricture. It does not give a very clear picture of the overall number of people presenting with the complaint of urethral stricture since not all patients get to be operated on. As a result, the proportion of urethral stricture may seem lower because it only involved those who were operated on while in fact the proportion of patients with urethral stricture might be higher. However, the focus of this study was only on those who were operated on for urethral stricture and thus data was collected from their case files accordingly.

### **Conclusion**

The prevalence of urethral stricture has been fairly constant over the period of five years and was seen mainly in the elderly aged sixty years and above. The cause of the urethral stricture was seen to be varying over the years between iatrogenic injury, trauma and infections. In the iatrogenic injuries, urethral catheterization was found to be the major culprit causing these strictures whereas in trauma, the majority were caused by road traffic accidents. The bulbar urethra was the most common affected site. Urinary retention and recurrent urinary tract infection were the most common complications seen. Urethrogram was the investigation most commonly used and the surgical procedure most preferred was DVIU.

Further studies need to be carried out in our country in order to obtain a clear picture on the burden of this disease as well as its trend over the years. A study with a longer duration may need to be conducted so as to notice changes in the trend of the disease that are clinically evident.

### **Conflict of interest**

Authors declare no conflict of interest.

### **Authors' contributions**

SS conceptualized the study, collected the data, carried out the study and ran the data analyses. SS also participated in writing the manuscript critically for important intellectual content prior to submission. MA read and approved the final draft of the manuscript for submission.

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