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The Short-Term Outcome of Urethral Stricture Disease Management in HIV and Non-HIV Infected Patients: A Comparative Study

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ABSTRACT

Purpose: This study intends to compare short-term outcomes of treatment of urethral stricture disease between human immunodeficiency virus (HIV) seropositive and HIV seronegative patients at the University Teaching Hospital (UTH) in Lusaka.

Methods: This was a prospective cohort study conducted on patients presenting with urethral stricture disease at the UTH, Lusaka, Zambia, between October 2009 and December 2010. One arm included HIV seropositive patients and the other arm had HIV seronegative patients. The recruited patients underwent urethral dilatation, anastomotic urethroplasty, and staged urethroplasty. They were followed-up postoperatively for 6 months, and recurrence and complication rates were compared between the 2 groups. Other parameters studied included patient demographics, cluster of differentiation (CD4) cell counts in positive patients, HIV World Health Organization (WHO) stages, stricture etiology, stricture sites, and stricture lengths. The collected data was analyzed using SPSS 16.

Results: A total of 71 patients with a mean age of 38.04 years who had urethral stricture disease were recruited for this study. Of the patients, 37% (26) were HIV seropositive while 63% (45) were seronegative, and 53.8% (14) of the seropositive patients were on highly active antiretroviral therapy (HAART). Of the urethral strictures, 45% (32) resulted from urethritis, and the prevalence of HIV in patients presenting with post-urethritis stricture disease was 50% (16/32). Of the strictures, 73.2% (N = 52) were located in the bulbar urethra, 19.7% (N = 14) were in the penile urethra, and 5.6% (N = 4) were located in the membranous urethra. Of the patients, 73% (N = 52) had urethral dilatation, 17% (N = 12) had anastomotic urethroplasty, and 10% (N = 7) had staged urethroplasty. The overall intraoperative complication rate was 2.8% (2) while postoperatively it was 12.7% (9); 55.2% (32/58) had urethral stricture disease recurrence after being followed-up for 6 months, with urethral dilatation accounting for most of the failures (28% [20/58]). Of the non-reactive patients, 47% (16/34) had recurrence while 67% (16/24) had recurrence. However, the 20% difference in recurrence between reactive and non-reactive patients was statistically insignificant ($P = 0.139$).

Conclusion: Urethral stricture disease affects patients from all age groups. The prevalence of HIV in patients with post-urethritis stricture disease is high. Stricture recurrence following treatment is not affected by the HIV status of the patient and CD4cc, although it is affected by stricture site and stricture length. Time to recurrence and cumulative survival of urethral stricture disease following treatment are also not influenced by the HIV status of the patient.

KEYWORDS: Aetiology, site, stricture, urethra

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INTRODUCTION

According to Steencamp et al. [17], urethral stricture disease is one of the oldest known urological diseases, and it remains a common problem with a high morbidity, despite earlier predictions to the contrary. In many third-world countries with limited medical resources, male urethral stricture disease remains highly prevalent [19].

Sexually transmitted infections (STI) are now the commonest group of notifiable infectious diseases in most countries, particularly in infants and those aged between 15 to 50 years. The control of STIs is important considering their role in increasing the transmission of HIV. STIs are hyperendemic in many developing countries, and urethral stricture disease and infertility are frequent sequelae in men [6].

Some STIs cause urethritis, which is etiology for urethral stricture disease, and urethritis is a risk factor for HIV transmission. The etiology of urethritis, the significance of potential pathogens, and the relation of urethritis to HIV infection were determined in 335 men (cases) with and 100 men (controls) without urethral symptoms. The seroprevalence of HIV was 45% in the patients with urethritis [18].

The term urethral stricture refers to an abnormal narrowing of the tube (urethra) that carries urine out of the body from the bladder. Barbagli [2] described the male urethral anatomy as a tubular structure about 18 cm in length, originating in the bladder, at the inferior and anterior level. After crossing the pelvic floor and the perineum, it runs along the entire length of the penis, ending at the apex of the glans. The male urethra can be subdivided into the prostatic urethra, membranous urethra, bulbar urethra, and the penile urethra. The urethra receives its blood supply from the bulbar arteries arising from the pudendal arteries and from the dorsal artery of the penis in retrograde fashion. The etiology of urethral strictures [3] includes insult to the urethral epithelium or the corpus spongiosum leading to narrowing of the urethral caliber. The cause of anterior urethral stricture disease can be classified into congenital or acquired. Acquired strictures are due to four main causes:

- Iatrogenic: These are hospital-acquired strictures. The traumatic placement of urethral catheters is the most common cause.
- Infection: Strictures are mostly due to gonococcal urethritis.
- Inflammation: Balanitis xerotica obliterans and lichen sclerosis are the causes. It usually begins with inflammation of the glans and inevitably causes meatal stenosis.
- Trauma: Urethral injuries occur mostly in association with pelvic fractures. The membranous urethra is prone to injury in pelvic fractures as it is posterior and inferior to the pubic symphysis.

Patients with urethral stricture disease become symptomatic only after the urethral caliber falls to less than 10 Fr [3]. They present with a history of obstructive voiding symptoms (poor flow, straining to void, incomplete bladder emptying, urinary retention), urinary tract infections, urethral bleeding, and now more rarely urethrocutaneous fistula and periurethral abscess development. Investigations aim to establish a diagnosis, identify coexisting infections, and determine the location and nature of the stricture in order to devise a treatment plan [3,9].

- Urine culture: A urine culture is mandatory to identify infection and to treat it before contemplating treatment.
- Urinary flow rate: It provides useful information during the initial assessment and follow-up.
- Flexible urethroscopy: This has simplified the evaluation of the urethra.
- The urethrogram: It is the single most important investigation when evaluating urethral stricture disease. It provides information on the site, length, number, caliber, and relation of the stricture to other structures.
- Ultrasonic evaluation: This is more accurate in deter¬mining spongiofibrosis.

Treatment of urethral strictures is primarily surgery, but the choice of the appropriate treatment is based on the characteristics of the stenosis (site, etiology, length, adverse local factors) and on the patient's characteristics (age, clinical history, associated diseases, physical and mental condition) [2]. The basic treatment types are:

1. Periodical instrumental and clinical evaluation of the patient. This approach is commonly known as watchful waiting.
2. Progressive dilatation of the urethral caliber, periodically performed in an outpatient office using soft catheters.
3. Endoscopic opening of the stricture. This procedure is commonly known as internal urethrotomy using a cold knife or holmium laser.
4. Surgical repair of the stricture. This procedure is commonly known as urethroplasty.

PATIENTS AND METHODS

Inclusion criteria included patients irrespective of age with urethral stricture disease confirmed by a urethrogram and with a maximum urinary flow rate (Qmax) less than 15 mls/min. They also had an HIV test done and had no complications on recruitment. HIV-positive patients had CD4 cell counts done.
Patients with strictures less than 1 cm long underwent urethral dilatation while anastomotic urethroplasty was done for strictures between 1 and 3 cm. Staged substitution urethroplasty was used for strictures longer than 3 cm.

The data obtained was entered into Windows Excel 2007 and then exported to SPSS version 16. Assessment of the association between dependent and independent variables was done using the chi-square test. Multivariable logistic regression analysis was used to determine the factors associated with stricture

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recurrence, and a time-to-recurrence analysis was performed using the Kaplan-Meier method and log rank score.

RESULTS

A total of 71 patients were recruited in this study. Of those, 36.6% (N = 26) were aged below 30 years, 31% (N = 22) were aged 31 to 40 years, and 32.4% (N = 23) were aged above 41 years. The minimum age was 4 years and the maximum age was 84 years, with 38.04 years being the mean. Furthermore, 63% (N = 45) of the patients were HIV positive while HIV negative patients accounted for 37% (N = 26). All HIV seropositive patients had HIV WHO stage I disease and 53.8% (N = 14/26) were on HAART.

Stricture Characteristics and HIV

Figure 1 shows that urethritis is the commonest cause of urethral stricture disease, as 45.1% (N = 32) had post-urethritis urethral stricture disease. Of the patients, 16.9% (N = 12) had stricture disease resulting from external trauma while 25.4% (N = 18) had urethral stricture disease resulting from unknown aetiologies. Iatrogenic trauma was the least common etiology and was an etiology in 12.7% (N = 9) of the patients.

Table 1 shows that the bulbar urethra is the commonest location of urethral stricture disease, accounting for 73.2% (N = 52). Furthermore, 5.6% (N = 4) had strictures located in the membranous urethra, and 19.7% (N = 14) had strictures in the penile urethra. The stricture was located in the bulbomembranous urethra in 1.4% (N = 1) of the patients.

Figure 2 shows that 76.0% (N = 54) of the patients had strictures less than or equal to 1 cm in length while 14.1% (N = 10) had strictures between 1.1 cm and 3 cm. Finally, 9.9% (N = 7) had strictures longer than 3 cm. As illustrated by Table 2, 50% (N = 16/32) of patients with post-urethritis stricture disease were HIV positive. Table 3 shows that 2.8% (N = 2) of the patients had intraoperative complications. The complications included pain, minimal bleeding, and mild haemorrhaging. Table 4 shows that 12.7% (N = 9) of the patients had postoperative complications, 4.2% (N = 3) had postoperative wound infections, and 8.5% (N = 6) had urethrocutaneous fistulas. Of the patients who had urethral dilatation, 52.5% (21/40) had recurrence while all patients (100%) had staged urethroplasty recurrence (Table 5). Anastomotic urethroplasty had the lowest recurrence percentage at 36.4% (4/11). In total, 44.8% (26/58) of the patients had no recurrence after being followed-up for 6 months, 55.2% (32/58) had recurrence, and 18.3% (13/71) were lost to follow-up.

Figure 1. Stricture etiology.

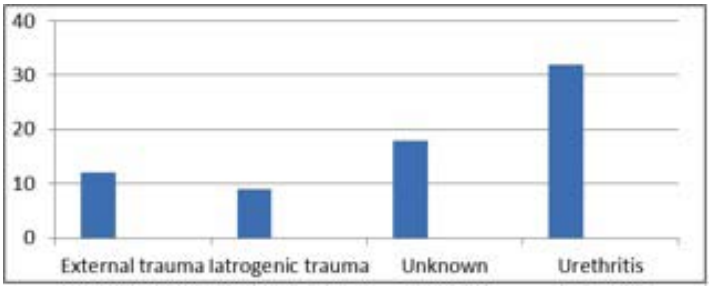
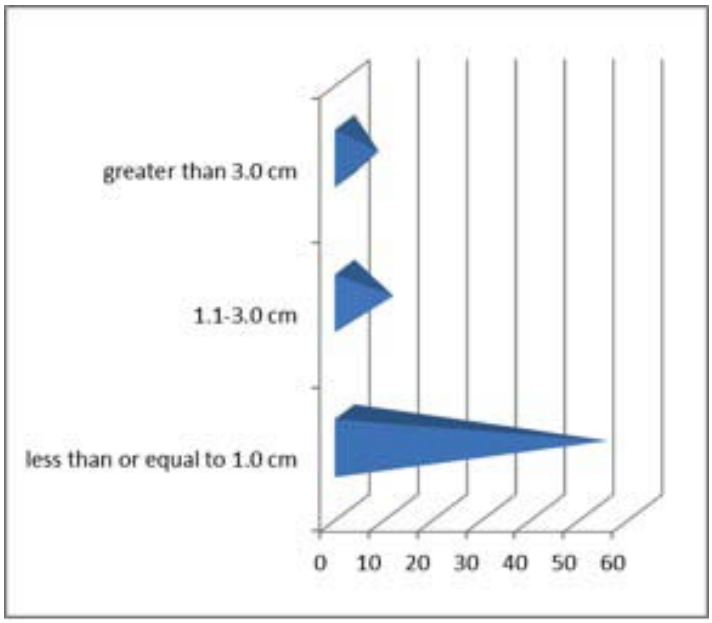


Figure 2. Stricture length.



Of the patients who had urethral dilatation, 36.2% (21/58) had recurrence while 6% (4/58) who had anastomotic urethroplasty had recurrence. Of the post-staged urethroplasty patients, 10% (7/58) had urethral stricture disease recurrence. Of the non-reactive patients, 47% (N = 16/34) had recurrence while 67% (N = 16/24) of the reactive patients had recurrence (Table 6).

Chi-square tests were carried out to determine the association between dependent and independent variables (Table 7). The

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Table 1. Stricture location..

	Frequency	%	Valid %	Cum. %
bulbar urethra	52	73.2	73.2	73.2
bulbomembranous urethra	1	1.4	1.4	74.6
membranous urethra	4	5.6	5.6	80.3
penile urethra	14	19.7	19.7	100
total	71	100	100	n/a

Table 2. Stricture etiology and HIV status crosstabulation..

		HIV status		Total
		non-reactive	reactive	
stricture etiology	urethritis	16	16	32
	iatrogenic trauma	7	2	9
	external trauma	9	3	12
	unknown	13	5	18
total		45	26	71

null hypothesis was rejected on association between recurrence and stricture length and stricture location.

Multivariable Logistic Regression Analysis

The multivariable logistic regression analysis (Table 8) was used to know the effect of independent variables on stricture recurrence. There was no statistically significant result.

Kaplan-Meier Plots

A time-to-recurrence analysis was done using the Kaplan-Meier method. Table 9 shows that 25% of the non-reactive patients took 55 days for stricture recurrence to occur while 25% of the reactive patients took 98 days for stricture recurrence to take place. Figure 3 places the cumulative survival at 50 days for non-reactive patients as being 0.3 and for reactive patients as being 0.55. The cumulative survival in most parts of the curve is higher in reactive patients.

Table 3. Intraoperative complications.

	Frequency	%	Cumulative %
no complication	69	97.2	97.2
pain and mild bleeding	1	1.4	98.6
mild bleeding	1	1.4	100
total	71	1.4	100

Table 4. Postoperative complications..

	Frequency	%	Valid %	Cum. %
wound infection	3	4.2	33.3	33.3
fistula	6	8.5	66.7	100
no complication	62	87.3	n/a	n/a
total	71	100	n/a	n/a

Table 5. Procedure type versus recurrence.

Procedure	Patients enrolled	Lost to follow-up	Completed study	Recurrence
urethral dilatation	52	12	40	21
anastomotic urethroplasty	12	1	11	4
staged urethroplasty	7	0	7	7
total	71	13	58	32

DISCUSSION

Sociodemographic Characteristics of Patients

The mean age of patients presenting with urethral stricture disease in this study was 38.04 years. This mean age is close to what is reported in other African studies. Shittu [15], in Nigeria, reported the mean age as being 42.2 years. Another study by Ramyil et al. [14] found the mean age to be 30.6 years. Heyns and Marais [10] showed that the mean age of patients presenting with urethral stricture disease was 48 years. Most patients were below 30 years old [11]. This is the most sexually active age group and most strictures can be attributed to urethritis.

Stricture Characteristics and HIV

In this study, urethritis was the commonest cause of urethral stricture disease as 45.1% (N = 32) of the patients had post-urethritis urethral stricture disease, 16.9% (N = 12) had stricture disease resulting from external traumsa, and 25.4% (N = 18) patients had stricture disease resulting from unknown etiologies. Iatrogenic trauma was the least common etiology and was an etiology in 12.7% (N = 9) of the patients. This conforms with other studies done in Africa that have shown urethritis as the commonest cause of urethral stricture disease. At the Urology Unit, Department of Surgery, University College Hospital, Ibadan, Nigeria, a study carried out indicated the etiology of stricture disease as being post-infective in 80% of the cases [15]. At the Urology Department of the Conakry University Hospital, Republic of Guinea, the majority of strictures were caused by infection followed by post-traumatic strictures, accounting for 84 and 10%, respectively [5].

The pattern, however, is different in developed countries. A study by Fenton et al. [7] in the United States of America found that most strictures were idiopathic (34%) or iatrogenic (32%); fewer were inflammatory (20%) or traumatic (14%). The high prevalence of post-urethritis urethral stricture disease is due to the high prevalence of untreated STIs where sequelae are urethral stricture disease. The lower percent of post-infective strictures in this study compared to other African studies may be because some participants felt stigmatized when mentioning urethritis as an etiology. Such participants' etiology thus fell under unknown causes.

In this study, the commonest location of urethral stricture disease was the bulbar urethra accounting for 73.2 % (N = 52). Of our patients, 5.6% (N = 4) had strictures located in the membranous urethra, and 19.7% (N = 14) had strictures in the penile urethra.

Table 6. HIV status versus stricture recurrence.

		No recurrence	Recurrence	Total
HIV status	non-reactive	18	16	34
	reactive	8	16	24
total		26	32	58

Table 7. Chi-square tests.

Hypothesis	Chi-square statistics	Degree of freedom	*P* value	Comment
recurrence and stricture length	10.0009	1	0.002	reject the null hypothesis
reccurence and stricture location	6.568	3	0.047	reject the null hypothesis

Table 8. Regression analysis.

Valuable	OR	*P*	(c-i)
stricture location	0.407	0.008	0.210-0.789
stricture length	1.946	0.199	0.705-5.377
stricture etiology	0.534	0.167	0.219-1.301
CD4cc	0.633	0.598	0.116-3.457
HAART	1.745	0.675	0.129-23.548
education	1.295	0.565	0.537-3.126
occupation	3.062	0.281	0.400-23.412
HIV status	2.900	0.037	1.069-7.870

The stricture was located in the bulbomembranous urethra in 1.4% (N = 1) of the patients.

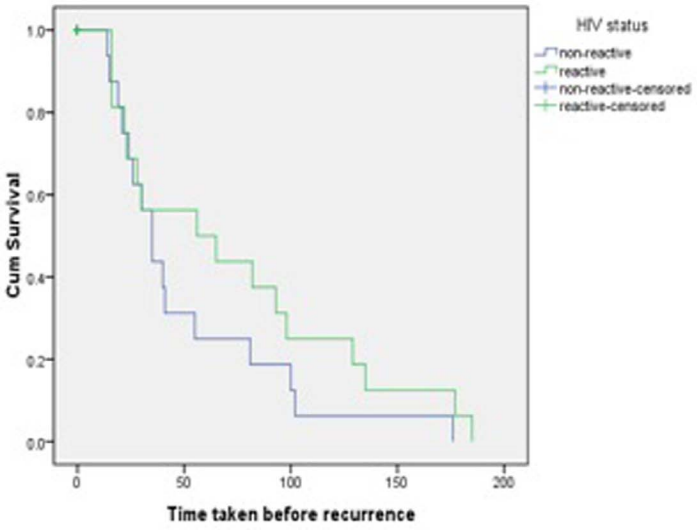
Ramyil and group [16] showed that strictures were bulbar in

Table 9. Kaplan-Meier percentiles.

	Est.	Std. error	Est.	Std. error	Est.	Std. error
non-reactive	55	34.641	35	4.961	21	4.330
reactive	98	31.177	56	35	22	6.062
overall	93	11.635	35	7.778	22	3.062

Est. = Estimate

Figure 3. Survival functions.



89%. The pattern was similar in the United States of America where Fenton et al. [7] found that most strictures involved the bulbar urethra (52%). Therefore, the pattern of stricture location in this study is similar to what is seen in other developing and developed countries.

Stricture length was important, as it determined the type of operation to undertake. Of our patients, 76.1% (N = 56) had strictures less than or equal to 1 cm in length, 14.1% (N = 10) had strictures between 1.1 cm and 3 cm, and 9.9% (N = 7) had strictures longer than 3 cm. The average urethral stricture length in this study was 1.4 cm. The average stricture length in a study by Fenton et al. [7] was 4.1 cm. The average stricture length in this study was lower than in the Fenton et al. study, and this may be because most strictures in this study were bulbar and mostly less than 1 cm.

The number of HIV seropositive and HIV seronegative patients was predetermined when calculating the sample size. Of the patients, 63% (N = 45) were HIV positive while 37% (N = 26) were HIV negative. The 2011 WHO HIV classification system was used, and all the patients who were HIV positive had stage I disease. Patients in this stage were either asymptomatic or had persistent generalized lymphadenopathy.

Patients with WHO stages II, III, and IV may not be fit for surgery. However, patients with WHO stages II, III, and IV were not excluded but were not available. The 2011 CDC HIV classification system was not used in this study as it is based on the lowest documented CD4 cell count and on previously diagnosed HIV-related conditions where details in the questionnaire were not captured.

In this study, 50% (N = 16/32) of patients with post-urethritis urethral stricture disease were HIV positive. This corresponds to a study done by Sturm et al. [18] who found the seroprevalence of HIV to be 45% in patients with urethritis. However, the study by Sturm et al. only considered urethritis and not urethral stricture disease, which is a sequelae of urethritis. This shows that the prevalence of HIV in patients with urethritis is high, as urethritis is a risk factor for HIV acquisition. STIs cause urethritis, which is an etiology for urethral stricture disease, and there is an association between urethritis and HIV.

Of the patients who were reactive, 53.8% (N = 14/26) were on HAART while 46.2% (N = 12/26) were not on HAART. HAART improves the immune status of patients by improving CD4cc, and this is a good predictor of a good surgical outcomes [12].

OPERATIONS AND OUTCOMES

Operations done included urethral dilatation, anastomotic urethroplasty, and staged urethroplasty. Of the patients, 73% (N = 52) had urethral dilatation while 17% (N = 12) underwent anastomotic urethroplasty; 10% (N = 7) had staged urethroplasty. In a study by Abdalla [20], the postoperative complication rate was 19%, and complications included secondary haemorrhage, ischemia, and sloughing of the penile skin and urethrocutaneous fistula. In this study, only 2.8% (N = 2) of the patients had intraoperative complications, which included pain, minimal bleeding, and mild haemorrhage. However, postoperative complications were seen in 12.7% (N = 9) of the patients and included wound infection and urethrocutaneous fistulae. The postoperative complication rate was lower than that highlighted in the study by Abdalla.

After following-up patients postoperatively for 6 months, the overall urethral stricture recurrence rate was 55.2% (N = 32/58). Overall, 36.2% (21/58) of the patients who had urethral dilatation had urethral stricture recurrence while 6% (4/58) of the patients who had anastomotic urethroplasty had urethral

stricture recurrence. Of the patients who underwent staged urethroplasty, 10% (7/58) had urethral stricture recurrence. Per procedure type, 52.5% (21/40) of patients who had urethral dilatation had recurrence while all patients (100%) had staged urethroplasty recurrence. Anastomotic urethroplasty had the lowest recurrence percent at 36.4% (4/11).

In a 5-year retrospective study by Nwofor and Ugezu [13], 51 patient records were reviewed, and it was found that urethroplasty gave better results with a 16.7% recurrence rate. Of the patients who had urethral dilatation, 61.5% required repeated dilatations between 6 and 12 months in order to maintain a satisfactory urine flow. The overall recurrence rate following urethroplasty in this study was 16% (6% for anastomotic urethroplasty and 10% for anastomotic urethroplasty), and this is similar to the recurrence rate in the study by Nwofor and Ugezu. The recurrence rate following dilatation was lower in this study probably because the follow-up period was shorter.

No known study has been done to compare urethral stricture disease management between HIV seropositive and seronegative patients. The overall urethral stricture recurrence rate in this study irrespective of HIV status was 55.2% (N = 32/58). With respect to HIV status, 47% (N = 16/34) of the non-reactive patients had urethral stricture recurrence while 67% (N = 16/24) of the reactive patients had urethral stricture recurrence. The difference in urethral stricture recurrence rates between reactive and non-reactive patients was 20%. There were more non-reactive patients (N = 34) than reactive patients (N = 24), and this contributed to the difference. However, this difference was also not statistically significant as there was no association in this study between urethral stricture recurrence and HIV status (P = 0.139).

Association Between Dependent and Independent Variables

Chi-square tests were carried out to know the association between dependent and independent variables. The null hypothesis was rejected upon the association between recurrence and stricture length and stricture location. The association between stricture recurrence and stricture length gave a chi-square test of 10.009 with 2 as the degree of freedom. The P value was 0.002, hence rejecting the null hypothesis. In the association between stricture recurrence and stricture location, the chi-square test was 6.568 and the P value was 0.047. The degree of freedom was 3, hence rejecting the null hypothesis. Therefore, there is an association between stricture recurrence and stricture location and length. However, there is no association between stricture recurrence and HIV status. In the association between urethral stricture disease recurrence and CD4cc, the chi-square statistic was 4.195 and the P value was 0.109. Therefore, there is no association between urethral stricture recurrence and CD4cc.

Multivariable Logistic Regression Analysis

Multivariable logistic regression analysis was used to know the effect of independent variables on stricture recurrence. All the independent variables could not fit into the model at once. The independent variables were fed into the model in batches and the results obtained were assembled into 1 table. This could be attributed to a small sample size. However, there was no statistically significant result.

Kaplan-Meier Plots

Analysis of the time-to-recurrence was carried out using Kaplan-Meier methods. Of the non reactive patients, 25% took 55 days to have stricture recurrence while 25% of the reactive patients took 98 days for a stricture to recur. This shows that HIV status in this study was not significant in determining stricture recurrence. This is further affirmed by the survival function curve, which showed the cumulative survival at 50 days for non-reactive patients as being 0.3 and for reactive patients as being 0.55.

CONCLUSION

Urethral stricture disease affects patients from all age groups, as the youngest patient in this study was 4 years old and the oldest was 84 years old. The commonest etiology of urethral stricture disease at UTH is urethritis. The prevalence of HIV in patients presenting with post-urethritis stricture disease is high.

The recurrence rate of urethral stricture disease following treatment is not affected by the HIV status and the CD4cc of the patient. However, urethral stricture disease recurrence is affected by the location of the stricture, length of the stricture, and the procedure used. The time to recurrence and cumulative survival of urethral stricture disease following treatment are also not influenced by the HIV status of the patient.

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