Outcomes of Patients Operated for Exstrophy-Epispadias-Complex at Tikur Anbessa Specialized Hospital and Menelik-II Specialized Hospital, Addis Ababa, Ethiopia

Thesis Submitted to Addis Ababa University, School of Medicine, Department of Surgery, Unit of Pediatric Surgery for Partial Fulfilment of the Requirement of Specialty Certificate in General Pediatric Surgery

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Declaration

I **Yeshigeta Hailemariam** declare that this paper is a result of my independent research work on the topic entitled "***Outcomes of Patients Operated for Exstrophy-Epispadias-Complex at Tikur Anbessa Specialized Hospital and Menelik-II Specialized Hospital, Addis Ababa, Ethiopia''*** in partial fulfillment of the requirements for specialty certificate for General Pediatric Surgery at Addis Ababa University, College of Health Sciences, Department of Surgery, Pediatric Surgery Unit. This work has not been submitted for a degree to any other university. All the references are also acknowledged.

Dr. Yeshigeta Hailemariam

Signature: _____

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Confirmation

This is to certify that Yeshigeta Hailemariam has carried out this research work on the topic entitled "***Outcomes of Patients Operated for Exstrophy-Epispadias-Complex at Tikur Anbessa Specialized Hospital and Menelik-II Specialized Hospital, Addis Ababa, Ethiopia***" under my supervision. This work is original in nature and has not been presented for a degree in any University and it can be submitted for the partial fulfillment of the requirements for the award of the specialty certificate for General Pediatric Surgery.

Dr. Woubedil Kiflu (Assistant Professor of General & Pediatric Surgery)

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Date: _____/_____/_____

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I also extend my thanks to all the people who have supported me to complete this research work directly or indirectly.

Abbreviations

ANC Antenatal care

BNR Bladder neck reconstruction

BOO Bladder outlet obstruction

EEC Exstrophy epispadias complex

IE Isolated epispadias

CBE Classic bladder exstrophy

CE Cloacal exstrophy

CPRE Complete primary repair of bladder exstrophy

EV Exstrophy variant

TASH Tikur Anbessa Specialized Hospital

MCRR Modified Cantwell Ransley epispadias repair

MH Menelik II Specialized Hospital

MSRE Modern staged repair of bladder exstrophy

PDA Patent ductus arteriosus

PFO Patent foramen ovale

SSI Surgical site infection

UCF Urethrocutaneous fistula

UTI Urinary tract infection

VCF Vesicocutaneous fistula

VUR Vesicoureteral reflux

YDL Young Dees Leadbetter

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Abstract

Background: Exstrophy epispadias complex (EEC) is a spectrum of congenital abnormalities that involves urinary system, musculoskeletal system, pelvis, pelvic floor, abdominal wall, genitalia, and sometimes the spine and anus. It encompasses epispadias, classic bladder exstrophy, cloacal exstrophy and other exstrophy variants. The management of EEC is primarily surgical. The surgical procedures are either functional anatomic reconstruction (single staged or multiple staged) and urinary diversions. The principal goals of surgical reconstruction in EEC are achieving urinary continence with volitional voiding, preservation of renal function, and functional and cosmetic external genitalia.

Objective: Describe the outcomes of patients operated for exstrophy epispadias complex at Tikur Anbessa Specialized Hospital (TASH) and Menelik II specialized Hospital (NH) from September 1st, 2012 up to August 31st, 2019.

Method: Retrospective descriptive study which assessed the outcomes of patients operated for exstrophy epispadias complex at TASH and MH from September 1st, 2012 until August 31st, 2019.

Results: One hundred and forty patients with EEC operated during study period, 91 patients (18 isolated epispadias, 66 classic bladder exstrophy, 3 cloacal exstrophy, and 4 variant exstrophy) were included in the study. No patient diagnosed during pregnancy. The median age at first hospital presentation was 5 months (birth to 12 years), and first operation was done at median age of 48 months (4 days to 12 years). The commonest type of EEC was classic bladder exstrophy (71.4%). Associated congenital anomalies was found in 26 (28.6%) of patients. Primary urinary diversions were done for 23 (25.3%) patients. Functional anatomic reconstructive procedures were performed for 68 (74.7%) patients. Most patients with classic bladder exstrophy have failed anatomic functional reconstruction and require urinary diversion to achieve continence. Early postoperative complications occurred in 76 (89.4%) patients. Forty-two patients (29 Mainz pouch II, 7 augmentation ileocystoplasty with catheterizable stoma, 5 epispadias repair and 1 complete primary repair of bladder exstrophy) achieved urinary continence. More than half (52.3%) patients disappeared from their regular postoperative hospital visits.

Conclusion: Urinary continence after anatomic functional reconstruction to EEC usually require urinary diversion (Mainz pouch II or augmentation ileocystoplasty) except in isolated epispadias.

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Chapter I: Introduction

1.1. Background

Exstrophy epispadias complex (EEC) is a spectrum of congenital abnormalities that involves urinary system, musculoskeletal system, pelvis, pelvic floor, abdominal wall, genitalia, and sometimes the spine and anus. It encompasses epispadias, classic bladder exstrophy, cloacal exstrophy and other exstrophy variants. (1)

Definitions:

Isolated epispadias (IE) is the least sever form of EEC which is characterized by partial or completely open urethral plate dorsally on the penis or between the clitoral halves in a girl.

Classic bladder exstrophy (CBE) is when the urinary bladder is an open plate through a lower abdominal wall defect with associated epispadias.

Cloacal exstrophy (CE) is the most severe form of malformation in the spectrum of EEC which is also known as omphalocele-exstrophy-imperforate anus-spinal (OEIS) complex. It is characterized by the urinary bladder and ileocecal junction of bowel are open plate at lower abdominal wall defect with truncated hind gut terminating at the perineum.(2)

Exstrophy variants (EV) involve several forms of abnormalities with partial manifestations of the above classic types of EEC. These includes covered exstrophy, superior vesical fissure, duplicated exstrophy, and other forms.(1, 3)

Pseudoexstrophy is when the malformation resembles classic form of exstrophy in regard to the facial and pubic symphyseal defects but do not have significant associated urinary tract anomaly. If these patients have associated isolated ectopic bowel segment, they are called covered exstrophy.(4)

In case of superior vesical fissure, only the upper part of urinary bladder is open in addition to fascial and skeletal defects of classic EEC. Anterior- posterior and side to side duplication of bladder with ectopic remnant bladder wall are known as duplicated bladder exstrophy.(1, 4)

Incidences and inheritance:

Exstrophy epispadias complex is rare congenital abnormalities with overall incidence of 1 in 10,000 live births and male to female ratio ranging from 1.5:1 to 6.0:1.(3, 5) The incidence of male epispadias is 1 in 117,000; female epispadias 1:484,000; classic bladder exstrophy 1:37,000; and cloacal exstrophy 1:200,000. (5-8) More than half of cases of bladder exstrophy can be detected prenatally in antenatal ultrasound examination.(8) The risk of bladder exstrophy in the offspring of individuals with bladder exstrophy and epispadias is 1 in 70 live births which is about 500 folds greater incidence than in the general population. The overall risk of recurrence of bladder exstrophy in a given family is 1%. (9, 10)

Etiopathogenesis:

The exact etiology and underlining embryologic mechanism EEC are not known. It is most likely multifactorial with both genetic predisposition and environmental factors are involved. Though there are several theories of pathogenesis of the exstrophy disease, the most widely accepted one is failure of mesodermal ingrowth between the two layers of cloacal membrane leading to premature cloacal membrane rupture. Depending on the timing of rupture, different forms of EEC are formed. (1-4, 9, 11)

Classification:

Exstrophy epispadias complex is classified (*Figure 1*) in to classic or typical form and atypical or variant exstrophy.(3) Classic bladder exstrophy is the most common type (60% of cases) of EEC followed by isolated epispadias (30% of cases). Cloacal exstrophy is rare which accounts only 10% of EEC. The atypical form or exstrophy variants are least common presentation of exstrophy diseases.(1) Covered bladder exstrophy, superior vesical fissures, duplicated bladder exstrophy, pseudoexstrophy, and different variants of cloacal exstrophy are some of the anomalies in the spectrum of EEC and considered atypical (non-classic) form of presentations.

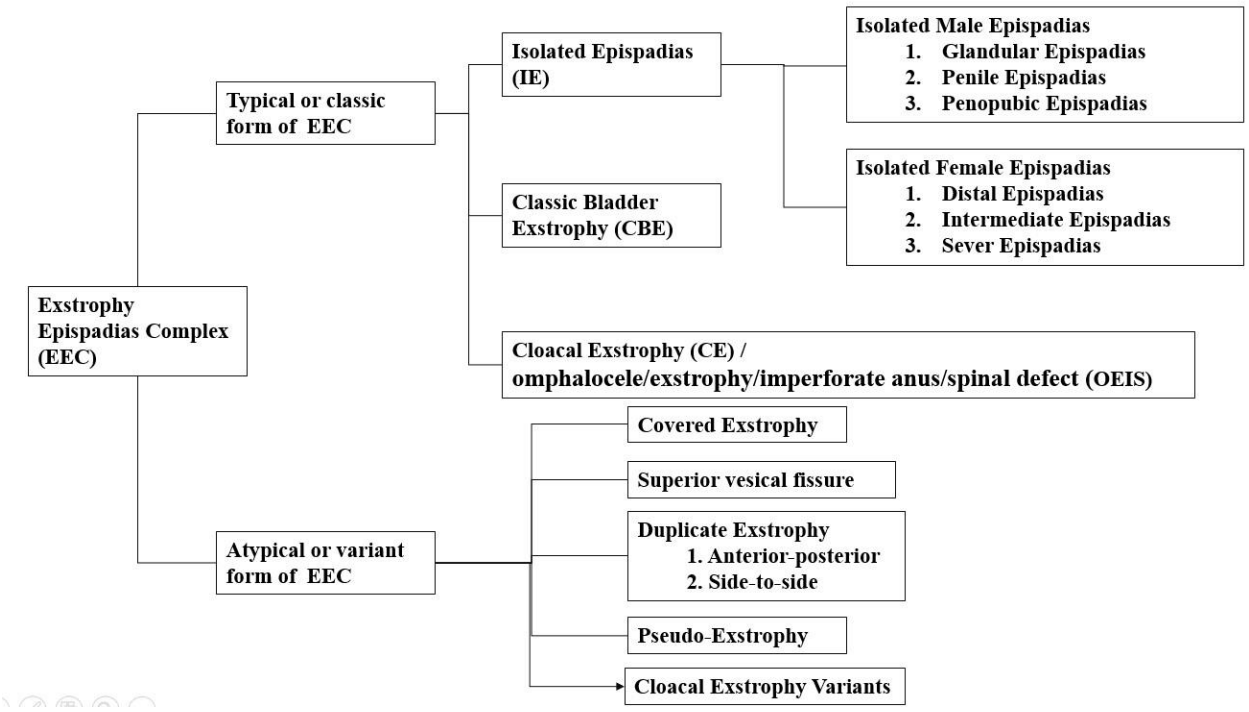

Figure 1: Classification of exstrophy epispadias complex

Diagnosis:

Prenatal detection of bladder exstrophy or cloacal exstrophy and male epispadias is possible by ultrasound and fetal MRI. The absence of bladder filling in the presence of normal kidneys and associated low-set umbilical cord suggests the diagnosis. The amniotic fluid volume is usually normal. Unfortunately, only approximately 25% of affected fetuses are diagnosed prenatally by ultrasound.(12, 13) Therefore most of the diagnosis are made postnatally with clinical examinations at birth.

Treatments:

The treatment of EEC is primarily surgical intervention. The principal goals of surgical reconstruction in EEC are achieving urinary continence with volitional voiding, preservation of renal function, and functional and cosmetic external genitalia. Prevention of urinary tract infections, urolithiasis, urinary tract malignancies, and preservation of the integrity of abdominal wall fascia and pelvic floor are some of the secondary goals of surgical interventions in exstrophy diseases.(1, 2, 4)

The surgical procedures for different components of EEC can be categorized in to functional anatomic reconstruction (single staged or multiple staged) and urinary diversions. There are several surgical techniques advised under each category. However, still in the twenty first century, no standard of care exists for this patient population.(14-16)

The two most popular isolated male epispadias repair techniques are Modified Cantwell Ransley epispadias repair (MCRR), and Complete Penile Disassembly (Mitchell's) technique. There are several techniques of female isolated epispadias reported in literature which includes transvaginal uretheral and bladder neck plication, uretheral twisting, bladder flaps, Marshall Marachetti vesicouretheral suspension with or without other continence procedures

Complete primary repair of exstrophy (CPRE) and Modern staged repair of bladder exstrophy (MSRE) are the two most popular functional anatomic reconstructive techniques in classic bladder exstrophy.

Modern staged repair of bladder exstrophy (MSRE) is the three staged procedure for anatomic reconstruction of classic bladder exstrophy. The first stage is bladder, abdominal wall, and posterior urethral closure with or without iliac osteotomy during neonatal period. The second stage is epispadias repair between the age of 6 months to 1 year. The third and last stage of MSRE is bladder neck reconstruction with anti-reflux procedure at the age of 5 to 7 years provided that adequate bladder capacity achieved and the patient is motivated to participate in the subsequent post-operative voiding program.

Complete primary repair of exstrophy (CPRE) is another technique of anatomical reconstruction of bladder exstrophy which includes closure of bladder, abdominal wall defects in conjunction with epispadias repair. It requires complete penile disassembly in male patient while in female the technique is similar to the first stage of MSRE. Most of the patients require further surgeries to achieve the goals of anatomic reconstructions of exstrophy diseases.(4)

1.2. Statement of problem

Exstrophy epispadias complex (EEC) is one of the most challenging clinical conditions encountered by pediatric surgeons and urologists. Most of the malformations in the spectrum of EEC require multiple surgeries with intense perioperative care and prolonged follow ups to achieve optimal outcomes.(2, 4, 9) Patients with EEC suffer both from the complications of the primary congenital abnormalities itself and also from the complications of surgical reconstructive measures provided for them. Multidisciplinary team approach is valuable in the care the patient.(17)

In African countries the affected patients are usually isolated from community and social engagements due to the fear of stigmatization which in turn increase the social and emotional complications. Since most exstrophy epispadias complexes are not life threatening, the presentation of patient might be so late reaching up to 6-9 years in African settings. Therefore, the social pariah and delayed presentations to health care is another burden which complicate the care of the such patients.(18, 19)

Although there is significant improvement in the outcomes of patients with EEC (in terms of achieving continence and good quality of life) in developed countries, it has still devastating outcomes with high morbidity and mortality in developing countries.(3, 20)

The patient load of EEC in the two teaching hospitals (i.e. TASH and MH) of Addis Ababa University is relatively significant given that patients from all parts of the country are referred to this hospital. However there are no researches done at these hospitals on the outcomes of patients with EEC except one article which was published almost seven years back on the management of classic bladder exstrophy.(19)

1.3. Significance of the study

This research will assess the surgical outcomes of procedures done for different anomalies in the spectrum EEC. It will point out the common complications of operative managements. It also describes the peri-operative care provided for the patients in surgical setting of the two hospitals. Furthermore, it identifies challenges in the patient care. In general, this research will provide information on the status of care of patients with EEC and can be taken as baseline data to optimize the care of patients with these complex anomalies.

1.4. Literature review

Congenital anomalies are among the top five leading causes of death globally in under five years children. More than 95% of deaths occur in low- and middle-income countries. It is estimated two-third of congenital anomaly health burden could be averted through surgical intervention.(21) In low- and middle-income countries, congenital anomalies are less likely to be detected during pregnancy and subjected for termination, rather most will be born with sever anomalies and die postnatally or live with formidable morbidities. (22) Exstrophy epispadias complex is one of the spectrums of congenital anomalies associated with significant morbidities and mortalities that almost always requires demanding surgical interventions with intensive perioperative care and prolonged follow ups.

Exstrophy epispadias complex causes sever distress to the patients as well as to the family due to the obvious physical anomaly and continuous urine leakage which is not socially acceptable. The modern techniques of management of different anomalies in the spectrum of EEC has improved with the focus changed to improvement of quality of life rather than only survival. However, high mortality and significant morbidity has persisted in resource limited and developing countries.(20)

As it has been described above, the goals of modern surgical repairs of exstrophy epispadias complex includes achieving continence while maintaining renal function, satisfactory cosmetic and functional results with high quality of life.(1, 3) Avoiding urinary tract infections, reducing risk of urolithiasis and malignancies of urinary tracts, and preserving abdominal wall fascia and pelvic floor are considered the secondary objectives of surgical reconstructions in EEC.(4)

There is no gold standard of care existed in the management of most anomalies in EEC though several surgical options are available. Many surgical techniques and options of management of different anomalies in the spectrum of EEC are available. However, there are several factors that should be taken in to consideration, especially in resource limited countries, whenever planning and choosing different options of managements. Some of these factors are the severity of abnormality, the experience of surgeon and anesthesiologist, the level of perioperative intensive care services, the possibilities and adherence of long term follow up, economic and

educational level of parents, and also the cultural expectations on the outcome of the anomalies. (1, 3, 4, 9, 17, 23)

Late presentation to hospitals is the common scenario in developing countries despite the obvious anomaly of EEC at birth. This may be due to lack of finance or because of cultural beliefs. Extreme late presentation will late the patient to miss the opportunities of important early interventions that affect long term outcomes.(19, 20)

1.4.1. Urinary continence

Urinary incontinence is one of the main sources of morbidities in patients with EEC. Therefore, urinary continence is one of the most important focus in the management of EEC. Though the definition of urinary continence widely varies, approximately 70% to 80% of children will become continent through the urethra with modern reconstructive techniques.(3, 24) However, intermittent urethral catheterization or urinary diversion is sometimes necessary to achieve dryness, especially in the sever forms of EEC. (17)

In the ideal set-up of developed countries, an overall 80% urinary continence rate is expected after functional anatomic reconstruction of EEC. Rosch WH et al, reported 72.3% complete urinary continence with spontaneous voiding after primary complete repair of EEC using Erlanger technique. This long-term outcome analysis also showed that urinary continence after redo repair of EEC is significantly low (42.5%). Therefore, successful primary repair is an important factor for bladder growth to attain adequate bladder capacity for BNR.(3, 25) The risk of urinary incontinence and the need for urinary diversion are both increased by failed initial closure and poor bladder growth.(26) Other factors that determine the surgical success of bladder exstrophy closure include a tension-free closure, free flow of urine, secure placement of suprapubic tubes and stents, wound care and avoiding infection, postoperative immobilization, and preventing raised intraabdominal pressure in the early postoperative days.(27)

Borer JG et.al, studied the success and complications in the first two years of CPRE on 27 patients (22 CBE, five epispadias) from February 2013 up to February 2015. There was no dehiscence in 27 patients (0%, 95% CI 0–12.5%). CPRE was done at a median age of 2.3 months (range 0.1–51.6). One boy had a hypospadiac urethral meatus at CPRE completion. Hydronephrosis of mild or moderate grade was present postoperatively in eight girls and two boys. Complications occurred in 6 girls (5 pyelonephritis, 4 urinary retention (BOO), 2

temporary CIC required, 1 Vesicostomy done and 1had bladder rupture. Only 3 boys were complicated among 14 CPRE on boys. Those were 1 pyelonephritis and 2 urethrocutaneous fistula.(28)

The importance of early initial closure was also emphasized by Husmann and colleague, who showed that only 10% of the patients who undergo bladder closure before 1 year of age but 40% of those who undergo the procedure at a later age require eventual augmentation.(29)

Mainz pouch II urinary diversion in children also provides very high primary continence rates. Pahernik, S. et al reported that 38 children with a mean age of 5 years were completely continent during the day and only 8.6% used pads during the night. Due to the modification of classic ureterosigmoidostomy in to low pressure pouch, upper tract function is usually preserved. However, 15.8% had episodes of pyelonephritis, and 14.5% needed ureteral reimplantation (due to stenosis in 10.1% and reflux in 4.4%). Sixty nine percent of patients need alkalizing drugs to prevent hyperchloremic acidosis, and therefore potentially impaired bone mineralization and growth deficiency.(30)

One previous report from TASH also showed high urinary continence rate after Mainz pouch II ureterosigmoidostomy. A 5-year retrospective review of medical records in TASH from 2007-2012 showed that staged procedure and Mainz II pouch ureterosigmoidostomy were the two procedures that were implemented for bladder exstrophy management. This study revealed that MAINZ-II is the viable procedure with high success of urinary continence (93.3%) to improve quality of life of patients with neglected bladder exstrophy.(19)

1.4.2. Perioperative complications

Depending on the severity of anomaly in the spectrum of EEC, and the type of procedures performed, several perioperative and long-term complications may occur. These complications include urinary incontinence, urinary tract infections with renal scaring, urolithiasis, malignancies, inguinal herniation, pelvic organ prolapse in females, inadequate penis in males with associated ejaculatory dysfunction and subsequent ejaculatory and psychosocial sequalae. Most of the above complications and urinary tract obstructions, bladder voiding dysfunction, abdominal wall incisional hernias and urocutaneous fistulas can occur in postoperative periods. If bowel segments are used in the reconstructions of anomalies or for

urinary diversions, several metabolic dysfunctions, bowel dysfunctions and perforations may complicate the postoperative periods of such patients.(4, 27)

In summary, the outcomes of EEC are relatively satisfactory in developed countries with ideal set-up, though the challenge and the demanding nature or the Problem is continued, but this is not the case in developing and low-income countries. Therefore, this research has paramount importance in sharing the experience in the two specialized hospitals to the other part of the world. It also gives the picture where we are in terms of achieving goals of management of EEC.

Chapter II: Objectives of the study

2.1. General objective

Describe the outcomes of patients operated for exstrophy epispadias complex at Tikur Anbessa Specialized Hospital and Menelik II specialized Hospital from September 1st, 2012 up to August 31st, 2019

2.2. Specific objectives

1. Assess the sociodemographic characteristics of patients with EEC
2. List the type of operative procedures done for patients with different type of EEC
3. Asses the common early post-operative complications of the procedures
4. Assess proportion of patients who achieved urinary continence
5. Assess proportion of patients who developed post-operative renal functional deterioration as described by elevated serum creatinine level
6. Explain the socioeconomic burden of EEC on the patients and care givers

Chapter III: Methods and materials

3.1. Study design

The study was a retrospective descriptive study design which has assessed patients operated for exstrophy epispadias complex at TASH and MH from September 1st , 2012 until August 31st , 2019 using structured questionnaire. Data were collected from patient medical record charts and from phone call interviews.

3.2. Study area and setting

The study was conducted at Tikur Anbessa Specialized University Hospital and Menelik II Specialized Hospital. TASH is the largest specialized hospital in the country that gets referral of patients from all parts of the country. Tikur Anbessa Specialized Hospital is currently serving as a teaching hospital for Addis Ababa University, College of Health Sciences. Pediatric Surgery Unit is one of the units of surgery department of the college. Pediatric surgery unit used to be the only pediatric surgery unit in the country that trains fellows and residents in pediatric surgery until recently. Menelik II Hospital is one of the oldest hospitals in Ethiopia. It is an affiliate hospital for Addis Ababa University where pediatric surgery service and training is being given.

3.3. Study participants

The study population were all patients with diagnosis of any components of epispadias exstrophy complex who were operated in Tikur Anbessa Specialized Hospital and/ or Menelik II Specialized Hospital, Unit of Pediatric Surgery from September 1st, 2012 up to August 31st, 2019.

3.4. Inclusion and exclusion criteria

All patients who were operated at either TASH or MH during the study period for any component in the spectrum of EEC and whose medical record charts were accessible for data collection were included in the study.

Those patients with the diagnosis of exstrophy epispadias complex who presented during the study period but not operated were excluded.

3.5. Data collection tool and procedure

Structured questionnaire was developed by investigator based on the literature reviews done to do descriptive analysis on the outcome of operative procedures for patients with EEC.

Initially the hospital record number and name of the patients with EEC operated during the study period sorted out from operation logbooks of the two hospitals. Then medical record charts of those patients collected from archive rooms. Data was filled on structured questionnaire prepared by primary investigator. Patients whose medical record charts were accessible had phone call interviews with the principal investigator to complete data not documented on their charts.

3.6. Variables

3.6.1. Dependent variables

The outcome variables called urinary continence status, post-operative serum creatinine level, and death were the dependent variables.

3.6.2. Independent variables

The independent variables used were age, sex, address, timing of diagnosis, age at first hospital visit, age at first operation, type of EEC, maternal antenatal follow-up status, setting of delivery, mode of delivery, school admission status, level of social interaction, post-operative follow up status, associated anomalies, and perioperative complications.

3.7. Data analysis and presentation

After data was collected using questionnaire, it was entered to a template prepared on Statistical Package for Social Science (SPSS) version 23. Then frequencies, mean, medians and cross tabulation between variables was done to describe variables. Chi-square test was performed to determine whether the variables are statistically independent or if they are associated.

The results are presented with tables and figures and corresponding explanation. Each pertinent finding was discussed to provide sensible interpretations.

3.8. Ethical clearance

Ethical approval was obtained from the Addis Ababa University College of health science, TASH Research Committee. The study ensured that all the information collected during the research were remained confidential.

3.9. Operational definitions

- ✓ **Urinary continence** is defined as dryness with either volitional voiding or intermittent catheterization for 3-hours or more intervals
- ✓ **Urinary incontinence** is either there is continuous urine leak or dry interval shorter than 3 hours.

- ✓ **Failed primary functional anatomic reconstruction** for EEC is when the primary planned operation (either single or multiple staged) develop any complication that require conversion to urine diversion procedures.

- ✓ **Renal function deterioration** is when serum creatinine level is elevated above the normal level after surgical procedure done for any anomaly in the spectrum of EEC.

- ✓ **Delayed initial hospital presentation** is when the first hospital visits for EEC beyond neonatal age (after 1 month of age).

- ✓ **Eligibility for assessment of urinary continence status;** If the child had continent urinary diversion (Mainz pouch II or augmentation ileocystoplasty with catheterizable stoma) or at least two years follow up after BNR for those functional anatomic reconstructions were done.

Chapter IV: Results and discussion

4.1. Results

4.1.1. Sociodemographic characteristics

There were total of 140 patients (108 males (77.1%) and 32 females (22.9%)) operated for EEC at TASH and MH from September 1st, 2012 up to august 31st, 2019. The male to female ratio is 3.4 to 1. Operative procedures for the 125 patients were done at TASH while the remaining 15 patients were operated at MH. Among 140 patients, a total of 91 (65%) patients' medical record charts were retrieved and included in the study (*Figure 3*).

The mother of two-third (66.7%) of the patients claimed to have antenatal pregnancy follow-up visits, but no patient was diagnosed during antenatal care (ANC) follow-ups. The age at their initial hospital visits ranges from the day of birth up to 12 years of age with median age of 5 months. They were operated at their median age of 48 months (range from 3rd day of life up to 12 years).

Patients were being referred to TASH and MH from different part of the country. Oromia region referred the highest number of patients (35.2%) followed by Addis Ababa (21.9%) and Amhara regions (21.9%). The total number of patients who came from these three regions was accounts 79.1% of the patients.

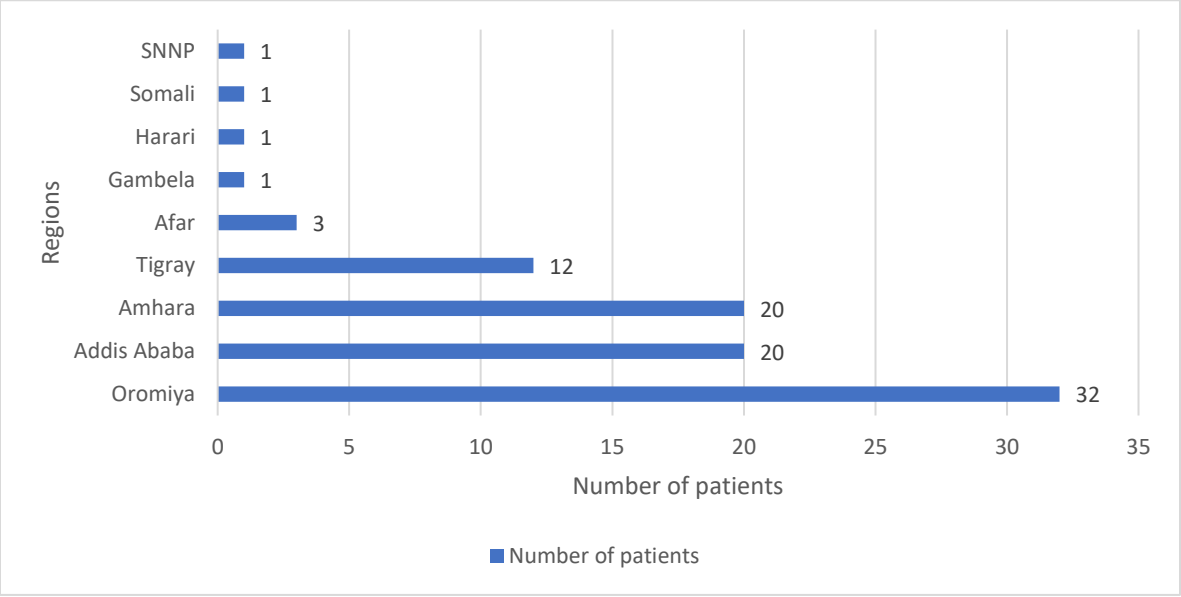

Figure 2: Birth places of patients with EEC

4.1.2. Type of exstrophy epispadias complex

The type of EEC in those operated patients were isolated epispadias in 33 patients, classic bladder exstrophy in 100 patients, cloacal exstrophy in 3 patients, and variant exstrophy in 4 patients. The variants of the exstrophy were 1 anterior-posterior duplicated bladder exstrophy and 3 covered exstrophies.

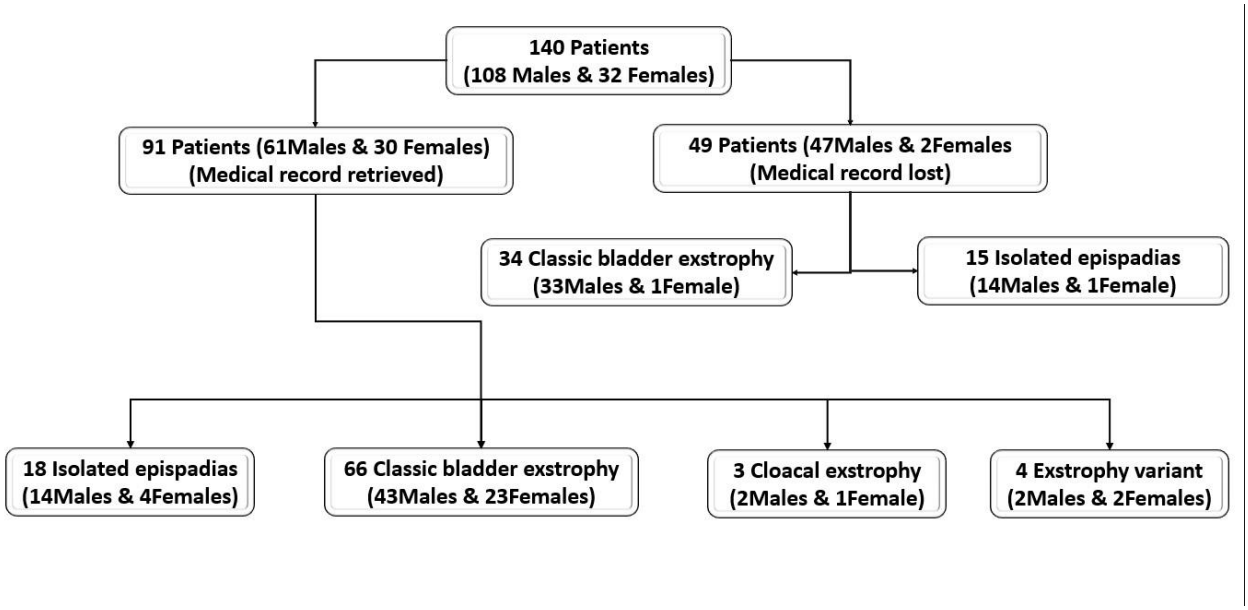

Figure 3: Type of EEC among patients operated during study period

4.1.3. Associated congenital anomalies

Among 91 patients included in the study, there were 26 (28.6%) patients with EEC who had associated anomalies (*Table 1*). Undescended testes were seen in 7 male patients. Inguinal hernias have occurred in 6 patients. The other associated anomalies seen include left renal agenesis (3 patients), congenital heart diseases (3 patients), Anorectal malformations (3 patients), hydronephrosis (2 patients), and intestinal duplications (2 patients). There was one patient with club foot associated with cloacal exstrophy.

Table 1: Associated anomalies in different types of EEC

Type of EEC	Associated anomaly	Number of patents affected	Remark
IE	Undescended testes	1	Bilateral
CBE	Inguinal hernia	6	5 bilateral and 1 unilateral
	Undescended testes	6	5 bilateral and 1 unilateral
	Renal anomalies	3	2 left renal agenesis and 1 hydronephrosis
	Anorectal malformations	2	Rectoperineal fistula
	Congenital heart diseases	3	2 PDA and 1 PFO
	Colonic duplication	1	
CE	Renal anomaly	1	left renal agenesis
	Club foot	1	Unilateral
EV	Anorectal malformation	1	Recto vestibular fistula,
	Colonic duplication	1	
Total		26	

IE; isolated epispadias, CBE; classic bladder exstrophy, CE; cloacal exstrophy, EV; exstrophy variant, PDA; patent ductus arteriosus, PFO; patent foramen ovale

4.1.4. Type of operative procedures

A total of 183 operative procedures under general anesthesia were done for the 91 patients with the average of 2 procedures per patient (ranges from 1-6). These include primary functional anatomic reconstructive procedures, urinary diversions (Mainz II pouch and augmentation enterocystoplasty with catheterizable channels), bladder neck procedures for urinary continence, and other procedures done for complications of planned surgeries of exstrophies.

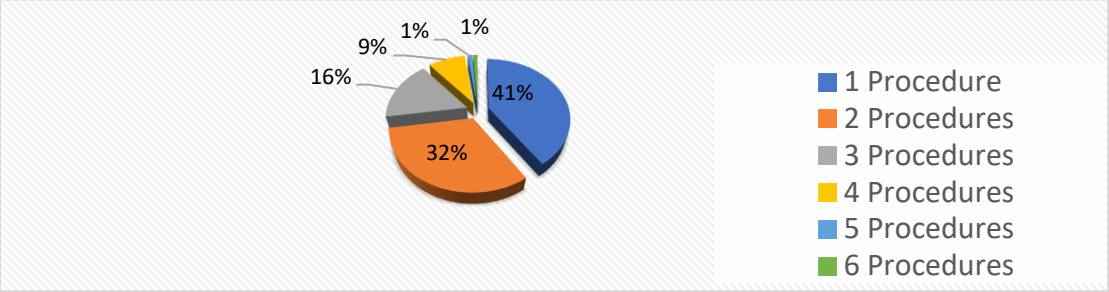

Figure 4: Number of procedures under general anesthesia per each patient

The initial operative managements among the 18 patients with isolated epispadias were; primary augmentation ileocystoplasty with catheterizable channel for 1 patient; Modified Cantwell Ransley epispadias repair for 13 patients; Mitchell's technique of epispadias repair was applied for one patient; and the remaining 3 were female epispadias repair. Two patients had conversion to urinary diversion (1 Augmentation ileocystoplasty and 1 Mainz II pouch) after primary repair has failed.

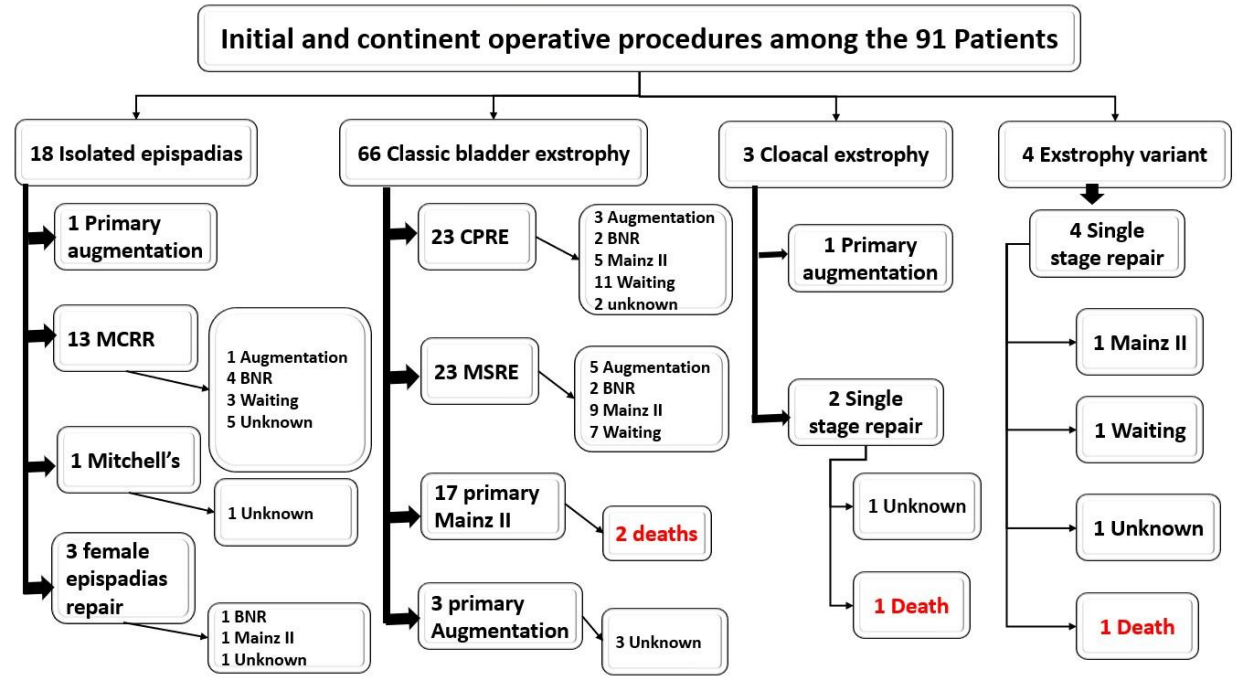

Figure 5: Initial and continent procedures in different types of EEC

***MCRR**; Modified Cantwell Ransley epispadias repair, **Mitchell's**; Mitchell's epispadias repair, **CPRE**; Complete Primary Repair of Exstrophy, **MSRE**; Modern Staged Repair of Exstrophy, **BNR**; Bladder neck reconstruction, **waiting**; waiting for continence procedure either due to their age or failed primary anatomic reconstruction, **Unknown**; unknown status about the continence procedure done or continence status due to loss from follow-up, **Mainz II**; ureterosigmoidostomy with Mainz II pouch.*

Among the 66 patients with classic bladder exstrophy, 20 (30.3%) primary urinary diversions (17 Mainz II pouch and 3 augmentation ileocystoplasty with catheterizable channel) and 46 (69.7%) functional anatomic reconstructions (23 CPRE and 23 MSRE) were done. Twenty-two (47.8%) among patients with classic bladder exstrophy, the functional anatomic

reconstructions failed and required conversion to either Mainz II or Augmentation ileocystoplasty with catheterizable channel (*Figure 5*).

There were 22 patients for whom primary anatomic reconstruction was done but waiting for further urinary continence procedures.

4.1.5. Early post-operative complications

Complications were documented in 76 (89.4%) patents. Surgical site infections, urinary tract infections, and wound dehiscence occurred in 58(63.7%), 50(54.9%), and 45(49.4%) patients respectively.

Table 2: The frequency of early post-operative complications in different operative procedures

SN	Complications	17 IE Repairs	23 CPRE	23 MSRE	33 Mainz II	14 Augmentation
1	SSI	9	18	17	11	3
2	UTI	10	12	16	9	3
3	Wound dehiscence	7	16	15	6	1
4	Post-operative hydronephrosis	4	9	8	7	
5	VUR	5	9	6	1	
6	UCF/VCF	1				
7	Inguinal hernia		1	4		
8	BOO/ urethral stricture	1		1		
9	Post-operative electrolyte disturbance			1	1	

***SSI**; Surgical site infections**, UTI**; urinary tract infections, **VUR**; vesicoureteral reflux, **UCF**; urethrocutaneous fistula, **VCF**; vesicocutaneous fistula, **BOO**; bladder outlet obstruction*

4.1.6. Status of primary functional anatomic reconstructive procedures

Among 91 patients, there were 68 (74.7%) patients for whom anatomical reconstructions (isolated epispadias repair for 17 patients, CPRE for 23 patients, MSRE for 23 patients, single stage cloacal exstrophy repair for 2 patients, and variant exstrophy repair for 4 patients) were done. From these patients, 25(36.8%) of them had confirmed failed primary anatomic

reconstructions that required conversion to either Mainz II pouch or augmentation enterocystoplasty with catheterizable stoma (*Figure 5*).

The initial procedures of failed anatomic reconstructive procedures were modern staged repair of exstrophy for 14 patients, complete primary repair of exstrophy for 8 patients, modified Cantwell Ransley epispadias repair for 2 patients and primary repair of exstrophy variant for 1 patient.

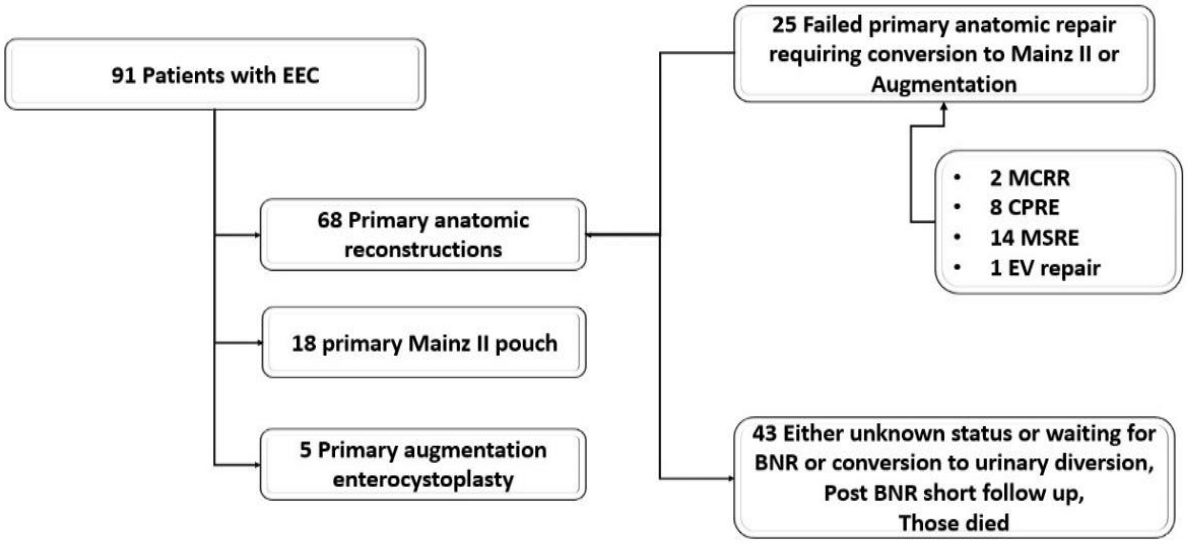

Figure 6: Failed primary anatomic functional reconstruction

4.1.7. Urinary continence status

Based on the most recent operative procedure done for the patients, only 52 patients are eligible to do assessment of urinary continence status (*Figure 7*). These are 33 patients after Mainz II pouch, 10 patients after augmentation enterocystoplasty with catheterizable channel, and 9 patients for whom BNR was done after anatomic repair of the EEC. **Two** patients with penile and glandular isolated epispadias were continent at the time of their initial presentation. There were 15 patients who discontinued their post-operative follow up visits and difficult to know their continence status. The remaining 22 patients were either waiting for continence

procedure to be done or had shorter than 2 years of post-operative follow up after continent bladder neck procedure.

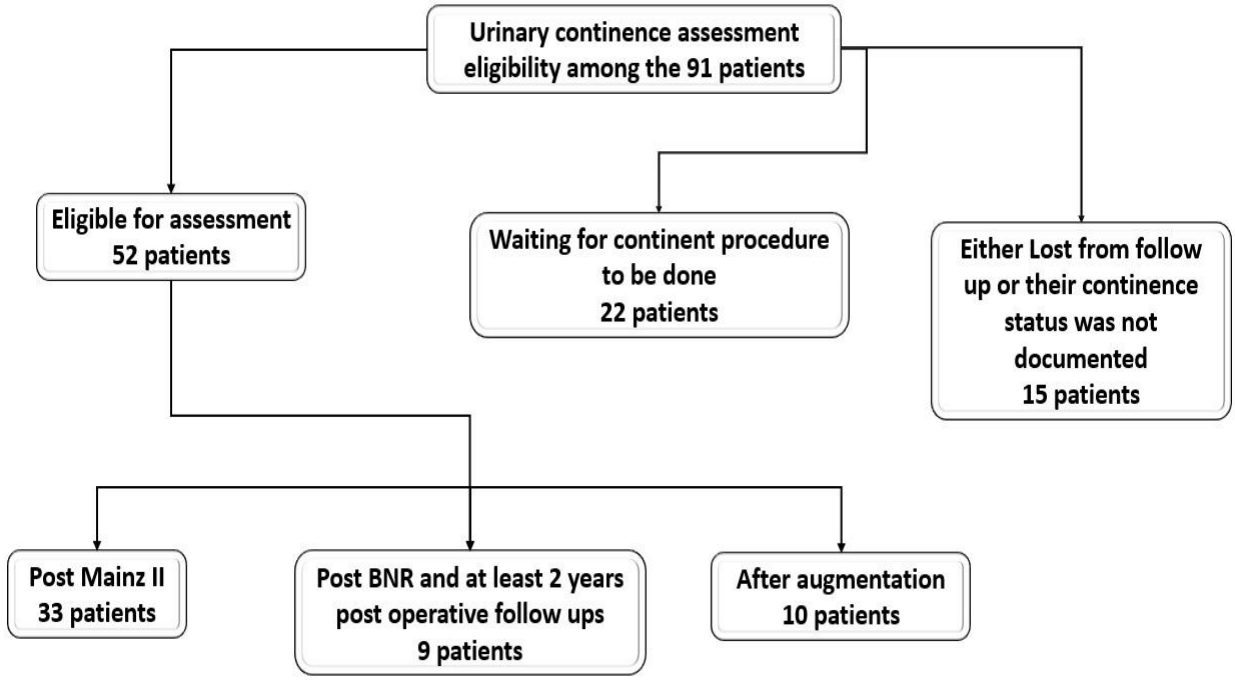

Figure 7: Eligibility for urinary continence assessment

From those patients eligible for assessment of urinary continence there were 42(80.7%) patients (29 after Mainz II, 7 after augmentation ileocystoplasty with catheterizable channel, 6 after primary anatomic reconstruction followed by BNR) have achieved urinary continence. The remaining 10 patients were either had continuous urine leak or dry interval less than three hours. Two of patients were with isolated epispadias were continent preoperatively and hence postoperative continence assessment was not applicable for them. The urine continence rate after Mainz II pouch ureterosigmoidostomy was 87.9% (29/33); augmentation ileocystoplasty with catheterizable channel was 70% (7/10); and after functional anatomic reconstruction with further BNR was 66.7% (6/9). Among continent patients after functional anatomic reconstruction with BNR, there was one patient with CBE for whom CPRE was done (*Table 3*), otherwise the diagnosis of the remaining 5 patients was isolated epispadias. The continence status of 4 patients for whom augmentation ileocystoplasty with catheterizable channel could not be assessed.

The procedures done for those 10 (19.2%) patients who didn't achieve dry interval for 3 hours or more were as follow. Four patients after Mainz II pouch ureterosigmoidostomy, three patients post augmentation ileocystoplasty with catheterizable channel, and three patients for whom functional anatomic repair and later bladder neck reconstruction was done.

Table 3:Primary and secondary procedures done for those who achieve urinary continence

Primary procedures	**Secondary procedures**	**Number of patients**
Primary augmentation ileocystoplasty		2
Primary Mainz II pouch		14
Incontinent isolated epispadias repair	BNR	5
	Mainz II	1
	Augmentation	1
Modern staged repair of bladder exstrophy	Mainz II	9
	Augmentation	3
Complete primary repair of bladder exstrophy	BNR	1
	Mainz II	5
	Augmentation	1
Primary repair of exstrophy variant	Mainz II	1
Total number of patients who achieved urinary continence		**42**

4.1.8. Post-operative renal functional status

Three patients with CBE had developed elevated serum creatinine level on their post-operative follow up visits. The first patient was after CPRE and the remaining two patients were after Mainz II pouch urinary diversion.

4.1.9. Mortalities

There were four recorded deaths among patients with EEC in the study period.

The first death was a female patient who died at 10 years of age. Mainz II was done for EV (covered exstrophy with small bladder) at 4 year. Bilateral ureteric reimplantation to Mainz II pouch was done for bilateral ureteric stricture.

The second death was for a patient with CE at 16 day of life after primary closure (cecal plate tabularization, anoplasty, omphalocele closure, bladder plate and abdominal wall closure) then re-laparotomy was done for ileal perforation at 6th post-operative day and died at 2nd day after re-laparotomy.

The third death was for patient with CBE at the age of 10 years, Mainz II was done at the age of 4 year, re-operated for bilateral ureteric re-implantation for bilateral ureteric stricture with elevated serum creatinine.

The fourth death was also for a patient with CBE at the age of 13 years, at 1 year after Mainz II done.

4.1.10. Socioeconomic burdens

No family history of similar condition was mentioned. About 66.7% had antenatal care follow up at their local health facility but none were diagnosed during prenatal follow-ups and 68% of patients were born at the health facilities.

There was delayed presentation to hospitals in 54.5% (48 patients) as defined by first hospital visits beyond neonatal age. The most common reasons mentioned for delayed presentation to the hospital were financial shortage for transportation, medical costs and accommodation, and lack of awareness about the availability of therapy which accounts 44.9% and 38%, respectively.

The total number of days that a patient admitted and stayed in hospital ranges from 4 days up to 124 days with average days of hospitalization of 37.9 days. About 52.3% were lost from regular post-operative follow up visits. The reasons mentioned for discontinuation of regular post-operative follow up hospital visits include financial shortage and frustration on the outcomes of the previously provided therapies.

Among children with EEC whose age is 5 years and above, 53.9% started attending school. Concerning their social interaction, 73.5% of parents of patients with EEC claimed to be good or excellent.

4.2. Discussion

Most of the anomalies in the spectrum of EEC are obvious to diagnose at birth. However, delayed presentation of patients to hospitals is one of the challenges in the care of patients with EEC in developing countries.(19, 31) This research showed us delayed presentations to health care and poor adherence to post-operative follow up hospital visits due to financial shortages is a common problem in our set up. The median age at presentation in our study is 5 months which is far beyond neonatal age, but it is lower than the previous reports from similar set-up. In the previous research done at TASH, the median age of presentation of patient with classic bladder exstrophy was 3.87 years.(19)

ANTENATAL DIAGNOSIS

The diagnosis of EEC usually made after birth, but may also be diagnosed with fetal ultrasound and MRI imaging.(3, 32) Prenatal diagnosis of EEC helps provide for prenatal counseling and optimal preinatal care and give chance to be delivered near centers where better neonatal care is available. It also helps to access early counseling service by experts who are familiar with such complex congenital malformations. Failure to diagnose during antenatal pregnancy follow-ups with subsequent delayed postnatal presentation will leads to unfavorable outcomes.(2, 31) In this study no patient with EEC was diagnosed prenatally though two third (66.7%) of them had antenatal care follow-ups. Similar experience was reported from Kenya.(31)

TYPE OF EEC

Classic bladder exstrophy is the most common type of EEC which accounts 60% of cases and followed by isolated epispadias and cloacal exstrophy, 30% and 10% of cases, respectively. (1, 15) In consistent with these literatures, the most common type of EEC operated in the two hospitals during the study period was CBE which accounts 71.4% (100/140) with male to female ratio ~ 2:1.

TYPE OF PROCDURES

The goals of surgical intervention in EEC cannot be achieved with single operative reconstruction in majority of cases, rather require multiple surgeries.(3, 4, 9, 15) Even in those surgical techniques for different malformations in the spectrum of EEC claiming single stage,

patients usually are subjected to further surgeries for suboptimal outcome or failed primary repair.(33) This need of multiple surgeries and prolonged follow ups and subsequent socioeconomical burden might be the reason for many patients lost from follow-up hospital visits. In our study, more than a quarter (27%) of the patients required three or more surgeries and with the average of two surgeries per patient. In addition, Majority of patients (52.3%) were lost from post-operative follow ups at different time.

Now a days, functional anatomic repair of EEC is considered as the gold standard in the surgical managements of such patient. However, there are also the supporter of primary urinary diversion.(16) There are several techniques applied to reconstruct different types of EEC.(3, 4, 9, 19, 34) Modified Cantwell Ransley epispadias repair, Mitchell's technique of epispadias repair and other female epispadias repair techniques were applied in the two hospitals for the management of isolated epispadias. Classic bladder exstrophy patients were managed either with Complete primary repair of exstrophy or Modern staged repair of exstrophy. The surgical techniques applied for cloacal exstrophy or other variants of exstrophy was dependent on the specific anomalies present. Mainz II pouch ureterosigmoidostomy and augmentation ileocystoplasty with catheterizable channel and YDL bladder neck reconstruction for those with favorable bladder capacity and age were the continent procedures performed in the surgical interventions of EEC in the two hospitals.

URINARY CONTINENCE STATUS

Even though variable success rate, about 80% overall urinary continence rate is expected from functional reconstructive repair of EEC.(3) Maruf et.al reported that only about 25% of patients are expected to void normally per urethra without reliance on catheterization or urinary diversion.(35) There are several institutional based reports of experience in this issue with different ranges of urinary continence rate after surgical repair for EEC.(3, 24, 35, 36) The report of urinary continence in patients with bladder exstrophy includes 67% after staged procedure from France, 72% after urinary diversion from Kenya, 69% after combined BNR and epispadias repair from USA, two reports with 92.3% and 93.3% after Mainz II pouch ureterosigmoidostomy from Ethiopia, and 72.3% after primary reconstruction from Germany.(3, 19, 24, 37-39) It is also difficult to compare urinary continence rate of different reports due to lack of standard

definition of urinary continence after repair for EEC.(40) The most commonly used definition of urinary continence is 3 or more hours dry interval.(33) This definition was taken in this study.

On the report of Kramer and Kelalis on the urinary continence of patients with isolated incontinent epispadias, 70% (37/53) of male and 83% (10/12) of female had achieved complete urinary continence.(41)

We found the urine continence rate of 87.9% (29/33) after Mainz II pouch ureterosigmoidostomy; 70% (7/10) after augmentation ileocystoplasty with catheterizable channel; and 66.7% (6/9) after functional anatomic reconstructions (5 IE repair and 1 CPRE) with further BNR. The finding of urinary continence after Mainz pouch II is comparable with the prior research in Ethiopia and with other similar settings. This research identified that most of our patient with EEC for whom primary anatomic functional reconstruction was done, achieve urinary continence after urinary diversion procedures (Mainz II pouch or Augmentation ileocystoplasty with catheterizable channel). Among 19 continent patients for whom either MSRE or CPRE was done, 18 of them required conversion to urinary diversion procedures (14 Mainz II pouch and 4 augmentation ileocystoplasty). It also showed that renal functional deterioration, as defined by elevated serum creatinine level, after repair of exstrophy or urinary diversions procedures is low.

ASSOCIATED ANOMALIES

Depending on the severity of exstrophy, associated anomalies occur with exstrophy epispadias complex. These associated anomalies include, urologic malformations in third of patients, other than the characteristics features of in the spectrum of exstrophy; spinal anomalies (7% in CBE and ~ 100% in CE). Gastrointestinal malformations may also be associated predominantly with the sever forms EEC. For example, cloacal exstrophy is associated with anatomic or functional short bowel syndrome in the 25% of cases. It is also associated with malrotations and intestinal duplications.(1, 3, 4) Inguinal hernia is one of the most commonly seen associated defect with CBE and CE. Stringer et. al, demonstrated the high incidence of inguinal hernia in classic bladder exstrophy with 86% male and 15% girls. Inguinal hernia in boys tend to complicate with incarceration in about 29% and 78% of the time it is bilateral condition.(9, 42) Inguinal hernia and undescended testes were the commonly encountered

associated abnormalities in this study. Sometimes associated anomalies may be the cause of deaths in patients with EEC depending of the severity of the malformations.(31)

According to Wiersma R., the mortality from bladder exstrophy was 42% (12/57 died in hospital) and concluded that the associated congenital abnormalities together with the impoverished environment result in a poor prognosis. He recommended that antenatal screening, early referral, and establishing urinary continence are factors that will improve the outcome in children with this condition in a Third World environment. In this study only 4 deaths out of 91 patients with EEC was recorded which is much lower than this report from South Africa.(20) Among the four mortalities in this study, three deaths (75%) were after Mainz II pouch ureterosigmoidostomy.

4.3. Conclusion and recommendation

Exstrophy epispadias complex is a spectrum of several complex congenital anomalies which requires dedicated multidisciplinary team to provide optimal patient care. There is no such team or specialized care services provided for patients with EEC in the two hospitals included in this study.

In conclusion, the diagnosis of most anomalies in the spectrum of EEC are made at birth. However, significant proportion of patients are presented to hospitals late beyond neonatal age. In addition, significant proportions of patients are lost from regular hospital follow up visits. The most frequently mentioned reason for delayed initial presentation to hospitals and disappearance from postoperative follow-up is financial shortage.

Unlike the most recent published literature, achieving urinary continence after functional anatomic reconstructions for different anomalies in EEC is found to be very low in this study. Most of the anatomic reconstructions end up with urinary diversions to achieve urinary continence except in isolated epispadias. However, urinary continence status after diversion procedures is comparable with similar setup.

Surgical site infections, urinary tract infections, and wound dehiscence were the most frequent early postoperative complications. Renal function is usually preserved in most of patients.

Three of the four deaths were after Mainz pouch II ureterosigmoidostomy was done.

Due to the heterogenicity of the anomalies and surgical procedures done for patients with exstrophy disease in this study, further prospective outcome researches of each operative procedure of different categories of EEC are recommended. Furthermore, standardizing operative procedures and establishing specialized perioperative and follow-up service may help us to accurately evaluate and optimize the patient care service.

4.4. Limitations of the study

There are different limitations to this study that may blur the conclusions and to give strong recommendations. These include retrospective study with accompanying large proportions of lost medical record charts of patients resulted in many missed data.

The heterogenicity of the anomalies in the spectrum of EEC and the variation of surgical procedure performed for each specific anomaly made the topic very wide.

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Annex

Questionnaire for assessment of outcome of patients operated for Exstrophy Epispadias Complex at TASH and MH-II

Sociodemographic Data

1. Card No_____
2. Name of patient_____
3. Age at first presentation to hospital_____
4. Age at first operation done for EEC_____
5. Age current to data collection_____
6. Gender
    a. Male
    b. Female
7. Family history of EEC
    a. Yes
    b. No
8. Living address condition
    a. Urban
    b. Rural
9. Maternal age_____
10. Maternal parity_____
11. ANC follow up status
    a. Had follow up
    b. Didn't have follow up
12. Mode of delivery
    a. SVD
    b. CS
13. Delivery setting
    a. Home
    b. Health facility

Socioeconomic Data

14. Family size in the household _____
15. Monthly Family income _____
16. Estimated cost (in ETB) spent for treatment _____
17. Delay to seek medical care (>1months)
    a. Yes
    b. No
18. Reason for delay to seek medical care
    a. Financial shortage
    b. Not aware of the treatment availability
    c. Delayed diagnosis
19. Total number of hospitalization (in days) _____

20. Post-operative follow-up status
    a. On follow-up
    b. Disappeared from follow-up
21. Reason for discontinued post-operative follow-up
    a. Financial shortage
    b. Change of following up hospital
    c. Due to frustration on treatment result
    d. Cured from diseases
    e. Not known
22. School admission status of patient
    a. Not started school yet
    b. Grade 1-6
    c. Grade 7-12
    d. College and above
23. How care provider grades the social interaction of the patient
    a. Excellent
    b. Good
    c. Limited
    d. Worst

Diagnosis and Associated anomalies

24. Best describing diagnosis
    a. Isolated epispadias
    b. Classic bladder exstrophy
    c. Cloacal exstrophy
    d. Exstrophy variant
25. Timing of diagnosis of the anomaly
    a. Prenatal
    b. Postnatal
26. Associated anomalies not included in the characteristic component of diagnosed EEC
27. Baseline Renal function (preoperative Serum creatinine level)
    a. Within normal level
    b. Elevated
28. Baseline Renal Ultrasound finding (Preoperative ultrasound)
    a. Normal
    b. Abnormality detected
    c. _____(specify)
29. Baseline serum electrolyte disturbance
    a. Yes
    b. No

Procedures and outcomes

30. Category of primary surgical intervention
    a. Single stage anatomic functional reconstruction of EEC
    b. Staged anatomic functional reconstruction of EEC
    c. Primary urinary diversion
31. Specific name of primary procedure done to manage EEC _____
32. Which further continent procedure has been done?
    a. BNR
    b. Bladder augmentation only
    c. Bladder augmentation with catheterizable stoma
    d. Anal sphincter-based procedure
    e. Not needed
33. Any early post-operative complication detected
    a. Yes
    b. No
34. Need of mechanical ventilation post operatively
    a. Yes
    b. No
35. Need of blood transfusion perioperatively
    a. Yes
    b. No
36. Surgical site infection (SSI)
    a. Yes
    b. No
37. Complete wound dehiscence
    a. Yes
    b. NO
38. Bladder prolapses
    a. Yes
    b. No
39. Bladder Perforation
    a. Yes
    b. No
40. Vesicocutaneous fistula (VCF)
    a. Yes
    b. No
41. Uretherocutaneous fistula (UCF)
    a. Yes
    b. No
42. Bladder outlet obstruction (BOO)
    a. Yes
    b. No

43. Vesicoureteral reflux (VUR)
    a. Yes
    b. No
44. Urinary tract infection (UTI)
    a. Yes
    b. No
45. Post-operative hypospadias
    a. Ye
    b. No
46. Post-operative dorsal penile chordae
    a. Yes
    b. No
47. Loss of penile tissue
    a. Yes
    b. No
48. Inguinal hernia
    a. Yes
    b. No
49. Incisional abdominal wall hernia
    a. Yes
    b. No
50. Use of CIC (clean intermittent catheterization) to void
    a. Yes
    b. No
51. Urolithiasis
    a. Yes
    b. No
52. Malignancy
    a. Yes
    b. No
53. Gait abnormality
    a. Yes
    b. No
54. Urine continence status
    a. Continent ($\geq$3 hours dry interval)
    b. Dry interval less than 3 hours
    c. Continuous urine leak
55. Hydronephrosis
    a. Yes
    b. No
56. Post-operative renal function (Serum creatinine level)
    a. Normal
    b. Elevated

57. Post-operative serum electrolyte disturbance
    a. Yes
    b. NO
58. Patient has expired with the cause related to the exstrophy disease
    a. Yes
    b. No
59. Secondary operative procedure (not initial plan)
    a. Yes
    b. No
60. Specific names of secondary procedures _____
61. Gait abnormality
    a. Not started walking
    b. Abnormal gait
    c. Normal gait
62. Epispadias presentation incontinence
    a. Yes
    b. No
63. Type of epispadias
    a. Female
    b. Glanullar
    c. Penile
    d. Penopubic
64. Clinical presentation of female epispadias
    a. Incontinence
    b. Abnormal genital appearance
    c. Incidental by health care provider
65. Factor for successful closure of female epispadias
    a. Bladder capacity
    b. Age at closure
    c. Severity of epispadias (mild, intermidate, severy)
66. Male epispadias
    a. Associated defects (chordee, pubic diastasis)
    b. Type
    c. Complication (incontinence, UTI, Impotence,VUR
    d. Chief compliants