Toward a better understanding of urinary fistula repair prognosis: Results from a multi-country prospective cohort study

Veronica M. Frajzyngier

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ABSTRACT

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This dissertation addresses several critical gaps in the evidence-base with regard to urinary fistula care and treatment in developing countries. First, I systematically reviewed and synthesized the small but growing body of literature examining the patient, fistula and facility-level factors that influence repair outcomes in developing countries. There was insufficient evidence to support a role of patient characteristics in influencing repair outcomes. In contrast, the weight of evidence suggested that some fistula characteristics, particularly scarring and urethral involvement, may influence the risk of failure to close the fistula, residual incontinence following closure and any incontinence. Results from randomized controlled trials examining prophylactic antibiotic use and repair outcomes were inconclusive, and observational studies examining the influence of peri-operative procedures were limited by small sample sizes and lack of statistical adjustment for potential confounding factors.

Secondly, using data from a multi-country facility-based prospective cohort study, I examined the prognostic value of five existing classification systems – those developed by Lawson, Tafesse, Goh, the World Health Organization (WHO) and Waaldijk – for predicting fistula closure, and evaluated the prognostic value of a score derived empirically from the data from this study. The scoring systems representing the Tafesse, Goh and WHO and empirically-derived classification systems were similar, and had the highest predictive values. However, none of the

scores evaluated achieved good discriminatory ability (AUC > 0.70), suggesting that other factors unrelated to fistula characteristics may be equally or more important in predicting repair outcomes.

Finally, I examined several issues surrounding two peri-operative procedures related to fistula surgery: abdominal versus vaginal route of repair, and catheterization duration greater than 14 days (compared to 14 days or less). Specifically, I explored the factors influencing the choice of these procedures, the influence of each of these procedures on repair outcomes independent of indication for repair or repair prognosis, and whether indication for the procedure or fistula prognosis moderates the influence of each of these procedures on repair outcomes. Abdominal route of repair was independently associated with site, parity > 3, and having a fistula that met indications for an abdominal route of repair (limited vaginal access due to extensive scarring or tissue loss, genital infibulation, ureteric involvement, or trigonal, supra-trigonal, vesico-uterine or intracervical location, or other abdominal pathology). Surgeon experience conducting complex repairs and mid-vaginal location were inversely associated with abdominal route of repair. Increased prognostic score was independently associated with catheterization > 14 days, as were site and surgeon experience doing complex repairs. Vaginal route of repair was independently associated with increased risk of failure to close the fistula, relative to abdominal route of repair; however, stratified analyses suggested that the risk of failed repair among those repaired vaginally may be particularly elevated among women who met common indications for abdominal route of repair. Duration of catheterization > 14 days was associated with failure to close the fistula, after adjusting for repair prognosis and surgeon experience; however, residual confounding by indication and reverse causation cannot be excluded as explanations for this finding.

Additional research is needed to confirm our findings regarding the discriminatory value of the classification systems evaluated. Further, since the value of a classification system lies not only in its discriminatory ability but also its reliability and ease of use, tests of inter- and intra-rater reliability of these systems are priority area for future research. Given the cost and health implications associated with abdominal route of repair and longer duration catheterization, additional studies examining the influence of these procedures on repair outcomes are warranted. Such studies must ensure adequate control of confounding by indication and prognosis of repair.

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Dedication

This work is dedicated to the men and women who have devoted their careers to improving the lives of women with obstetric fistula, and to the women themselves, who bravely persevere despite the hardships they face.

Chapter 1 : Introduction

Vaginal fistula is a devastating condition. The immediate manifestation of the condition is persistent leakage of urine or feces, or both; secondary consequences include a range of co-morbidities, and social marginalization. While the exact prevalence of the condition is unknown, it is estimated to affect thousands, if not millions, of women in developing countries. The primary cause of a vaginal fistula is prolonged obstructed labor; such cases are termed "obstetric" fistula. Obstetric fistula can be prevented through adequate access to emergency obstetric care; indeed, the condition does not occur in developed countries, where such care is readily accessible. Where surgical repair services are available and financially accessible, 80-95% of vaginal fistula can be closed surgically.[1] However, factors such as lack of provider expertise and the complexity of the repair can hinder the successful closure of a fistula. Moreover, up to 33% of women may suffer residual incontinence even after successful closure of the fistula,[2, 3] and an unknown percentage suffer complications or health-care associated infections related to intra- and post-operative procedures.

The issue of vaginal fistula has recently begun to garner worldwide attention, as well as funding from bilateral (e.g. USAID) and multilateral (e.g. UNFPA) donors. Nonetheless, a paucity of research on the topic remains, including research on effective treatment for the condition and factors influencing the prognosis of the repair. In this introductory chapter, I first describe the epidemiology and consequences of fistula and the context in which fistula repair takes place. I next illustrate the importance of developing an evidence-based standardized system for classifying the prognosis of fistula repair for both research and clinical purposes, and briefly review current gaps in knowledge with regard to two peri-operative procedures: route of surgical repair, and duration of catheterization.

Epidemiology and social consequences of vaginal fistula

The leading cause of fistula in the developing world is obstructed labor. The pressure of the fetus's head causes ischemic pressure necrosis and a slough of tissue, giving way to a hole between the vagina and bladder, or between the vagina and rectum. While less common, vaginal fistulas are also caused by sexual violence, particularly the insertion of foreign objects into a woman's vagina. Finally, vaginal fistula can occur as a result of malignant disease, radiation therapy or surgical injury (most often to the bladder during hysterectomy); the latter is the predominant type of vaginal fistula seen in industrialized countries. Fistula resulting after surgical injury is a relatively simple injury in comparison with fistula produced by obstructed labor: it is characterized by discrete wounding of otherwise normal tissue, whereas obstructed labor results in a massive injury with an area of central necrosis, surrounded by dense scarring.[4]

A vaginal fistula can occur in various areas of the reproductive tract, with the location depending on the point at which labor became obstructed. Most commonly, fistulas occur at the bladder; these are termed vesico-vaginal fistulas (VVF). Fistulas can also occur at the uterus (termed utero-vesico fistulas), in the cervix (cervico-vaginal fistulas), at the urethra (urethra-vaginal fistulas) or at the ureter (uretero-vaginal fistulas); diagrams of vesico-vaginal and uretero-vaginal fistulas are shown in Appendix A. Each of the above locations is associated with urinary incontinence, and the overarching term "urinary fistula" is often used to describe them. Finally, fistulas affecting the rectum are termed recto-vaginal fistula (RVF), and these manifest in fecal incontinence. As will be discussed in this dissertation, the location and characteristics of the fistula may determine the difficulty and the outcome of the surgical repair.

While the primary cause of vaginal fistula in developing countries is obstructed labor, the underlying causes include poverty, malnutrition, lack of access to emergency obstetric care and family planning, lack of education, early marriage, and low social status of women.[5] Malnutrition and early childbearing in particular both lead to increased risk of cephalo-pelvic disproportion, a primary cause of obstructed labor.[6] Indeed, surveys conducted in Nigeria,[7-9] Ghana[10] and Ethiopia[3] have shown that fistula patients are predominantly young, married at an early age, are of short stature, and receive very little education. Once a woman experiences an obstructed labor, the problem can be solved by caesarean delivery; however, timely access to emergency obstetric services is rare in developing countries.[11] Without access to such services, women with obstruction may labor for up to 5 days without effective intervention.[1, 9, 12]

To date only one large-scale, prospective, population-based study examining incidence of fistula in a developing country setting has been conducted, and the results of this study (124 cases of fistula per 100,000 deliveries, 95%CI 15-446) are difficult to interpret, as information about how the outcome was measured was not provided, and the sampling error is wide.[13] Recently, questions regarding lifetime experience of fistula symptoms have been included in Demographic and Health Surveys, and estimates of lifetime prevalence have ranged from 0.2% in Mali[14] and Niger[15] to 4.7% in Malawi.[16] However, these estimates must be interpreted with caution, due to problems related to questionnaire design (inappropriate contingency questions or lack of specificity in the definition of fistula), or underreporting of fistula symptoms (due to the social stigma associated with the condition).[17] Model-based estimates have also been developed, using assumptions about obstructed labor rates in developing countries; using this method, it is estimated that there are 82,000 fistula cases annually (8.68 per 100,000 women), and 654,000 prevalent cases (51.35 per 100,000 women) in developing countries.[18]

While the prevalence of the condition is unknown, the physical, social, and economic consequences of fistula are indisputably dire. The majority of women with fistula develop painful rashes as a result of the constant leakage of urine. In addition, women with fistula may develop amenorrhea, vaginal stenosis (narrowing of the vagina due to a build-up of scar tissue), infertility, bladder stones, and infection; they may also suffer concomitantly from leg weakness and footdrop (paralysis or weakness of the dorsiflexor muscles of the foot and ankle, resulting from compression of the sacral nerves by the fetal head as well as damage to the perineal nerve).[4] Women with fistula are often deemed to have an offensive odor, due to the constant leakage of urine and / or feces. As a result, they are often abandoned by their husbands, and are ostracized by their families and communities. In some contexts, community members may not understand the cause of fistula, may view the smell as resulting from poor personal hygiene, or may even view the injuries as punishment from God or as a form of sexually transmitted infection, further contributing to the woman's marginalization.[4] After development of the fistula, married women are frequently sent back to their parents' home, where they are precluded from cooking food, participating in social events or performing religious rituals.[19] For these reasons, women with vaginal fistula have been deemed "the most dispossessed, outcast, powerless group of women in the world."[20]

Treatment of vaginal fistula

The majority (80-95%) of fistulas can be closed surgically.[1] The method of treating obstetric fistula varies according to how soon a patient presents for care after obstructed labor. Early catheterization of women who start leaking after obstructed labor is increasingly being employed, and has been shown to cure up to one-fifth of early stage fistulas.[8] However, the majority of women present months or even years after a fistula has fully developed;[1, 9, 21] in this case, surgical closure is the only therapeutic option.

While many fistula surgeons have developed their own methods through experience,[22] the following methods described by John Kelly (1994), a fistula surgeon, are an example of typical procedures used for the repair of a simple vesico-vaginal fistula. The repair is approached either abdominally or vaginally, often depending on the surgeon's preference (gynecologists often prefer vaginal approaches, and urologists abdominal approaches) and the site of the fistula (low vesico-vaginal fistulas and urethra-vaginal fistulas are most often approached vaginally). For a vaginal approach, patients are placed in a lithotomy or knee-chest position. In the context of scarring and limited access, an episiotomy and division of scar tissue may provide better exposure for the repair. The fistula is mobilized, scar tissue is excised, and then the repair is performed with two layers of sutures. A catheter is inserted for 14 days to allow for continuous bladder drainage, and a dye test is performed to test whether the fistula has been closed, and that another fistula has not been missed.[23] Women are counseled to avoid sexual activity and inserting anything into the vagina for three months, and are generally discharged soon after catheter removal.

A number of challenges are associated with providing fistula repair services in developing countries. Specialized training and skills are necessary, especially to handle more complex cases, and this limits the availability of services. Women with the condition are predominantly poor and from rural areas, and often cannot pay for surgery or transport to a service site. Thus, fistula repair services must be provided free of charge. Fistula services are few and far between in Africa and Asia: the availability of services depends not only on the availability and motivation of surgeons with specialized skills, but also the availability of operating rooms, equipment, and funding from local or international donors to support both surgeries and lengthy post-operative care. In most contexts, the need for repair services exceeds the available human and infrastructural capacity. Moreover, the prolonged bladder catheterization that is frequently employed after surgery translates into a need for longer hospitalization, more intensive nursing care, increased costs, and thus decreased capacity for treating other patients. In light of these challenges, finding ways of providing services in a more efficient and cost-effective manner, without compromising surgical outcomes and the overall health of the patient, is paramount. To this end, further research on factors predicting successful repair, particularly those factors contributing to increased hospital stay and risk of infection, is needed.

Importantly, any research efforts examining the comparative effectiveness of different modes of service delivery (facility-level factors) must account for potential confounding by patient and fistula characteristics; moreover, the influence of facility-level factors may vary across different levels of fistula severity or prognosis, as characterized by patient and fistula characteristics

(Figure 1.1). A standardized evidence-based system for classifying the prognosis of a fistula repair surgery, as described below, would facilitate the conduct of such research.

Classifying fistula prognosis

Efforts have been made to develop a schema for classifying fistulas since the work of J. Marion Sims in the mid-19th century.[24] Currently at least 25 systems for classifying fistula are being used.[25] These classification systems have been developed through the efforts of individual surgeons, informed by their clinical expertise and experience. Fistula surgeons often use the classification system used or developed by the individual by whom they were trained. For instance, Nigerian surgeons who have been trained by Kees Waaldijk, a prominent fistula surgeon who primarily works in Nigeria, may use the Waaldijk classification system, while surgeons trained at Addis Ababa Fistula Hospital in Ethiopia may use the Goh or Tafesse classification systems. These classification systems may be used for didactic purposes, as well as for patient triage at the time of the patient's admission examination: for instance, classification systems can help determine if cases should be referred to specialized facilities, or which cases can be repaired by less experienced fistula surgeons.

Fistula classification systems vary in the type and amount of information collected, with some systems simply describing the location of the fistula, and other more detailed systems describing the anatomical structures affected and the extent to which these structures are affected, the location of the fistula described by fixed reference points, as well as other factors, such as bladder size, the size of the fistula and the amount of scarring involved. Disagreement remains with regard to which anatomical structures and fistula characteristics should be captured within a classification system. While most of the recently developed systems assess the presence of circumferential injury (complete separation of the urethra from the bladder), fewer assess other involvement of the urethra. Similarly, not all classification systems assess the size of the fistula, scarring, involvement of the bladder, and whether or not a prior repair was conducted; even fewer assess the degree of tissue loss, whether or not the vesico-vaginal fistula was accompanied by a recto-vaginal fistula, or the number of fistulas. For prognostic purposes as well as to further research in the field, a standardized classification, whereby each component of the system has been empirically demonstrated to independently predict repair outcomes, is needed. No commonly used classification systems are scoring systems, and none have clear thresholds defining a "simple" versus "complex" repair.

Rationale for a standardized evidence-based classification system

A standardized evidence-based system for classifying fistula prognosis would have a number of advantages. While extant classification systems may currently be used for triage purposes, an *evidence-based* system of classifying fistula prognosis may facilitate this process in terms of improving the accuracy of surgeon triage decisions. A prognostic scoring system would be particularly useful. Such a score could provide clear thresholds to guide triage decisions. For research and evaluation purposes, such a scoring system would facilitate the comparison of surgical outcomes across facilities, would provide a method of adjusting for confounding by prognosis of repair, and would facilitate comparative analyses of studies that examine treatment outcomes. Moreover, since clinical trials on fistula management may use fistula complexity as criteria for trial inclusion, an evidence-based index of complexity index will assist with participant selection.

There are several steps required in order to develop an evidence-based score for predicting the prognosis of fistula repair prognosis. First, it is necessary to determine which fistula characteristics are independently predictive of surgical outcomes. Identifying the minimal set of variables required for an accurate prognosis is also important, since the simpler a classification system is, the more likely it is to be adopted and used. This set of variables can then be transformed into an index or score. A commonly used method of creating a prognostic score is that developed by Hutchinson and Thomas,[26] whereby effect estimates calculated from beta coefficients are used to create a single variable prognostic of future risk. In Chapter 2, I evaluate the predictive value of classification systems developed by Waaldijk,[27] Lawson,[28] Tafesse,[29] Goh,[30] and a system presented by the World Health Organization (WHO) in their 2006 manual *Obstetric Fistula: Guiding principles for clinical management and programme development*;[31] in order to do so, I first transform each of these systems into prognostic scores. I also develop an empirically-derived prognostic score informed by the above systems. In chapter 4, I use this score to statistically adjust for confounding by prognosis of repair in the evaluation of the influence of duration of catheterization on repair outcomes.

The influence of route of repair and duration of catheterization on urinary fistula repair outcomes

Evidence with regard to the influence of peri- operative procedures on repair outcomes is lacking. Two procedures are of particular interest: abdominal route of repair, and duration of catheterization. Each of these procedures is associated with longer-term hospitalization, and therefore a potentially elevated risk of nosocomial infection (particularly urinary tract infection, or UTI[32]) and increased financial and human resource requirements.[33]

There are conflicting recommendations regarding whether a vaginal or abdominal surgical approach should be taken in the context of a complex repair. The vaginal approach may be associated with less blood loss and pain, fewer complications, and a shorter hospital stay; however, it may also be associated with vaginal shortening and scarring.[25] While certain fistula characteristics may indicate an abdominal repair, the choice of surgical approach remains to some extent a matter of surgeon preference or training. Though three studies[34-36] have examined whether surgical approach influences fistula repair outcomes, each were underpowered to detect small differences, and did not account for a range of potential confounding factors, such as the prognosis of, or indication for, repair.

There is similar disagreement regarding the optimal duration of catheterization following surgery. While surgical publications state that bladder drainage through catheterization should continue between 10 and 14 days post-operatively,[23, 37] this practice is based on tradition, rather than empirical evidence.[4] Indeed, a recent survey of 49 fistula surgeons conducted by Arrowsmith and colleagues[38] found that catheterization durations ranged from 5 to 21 days. Only one study on duration of bladder catheterization following obstetric fistula surgery has been published to-date. Nardos et al.'s (2008)[33] retrospective study of 212 obstetric fistula patients found no difference in the proportion of repair breakdown between those catheterized for 10 days (group 1), 12 days (group 2), and 14 days (group 3) at the Bahir Dar Hamlin Fistula Center in

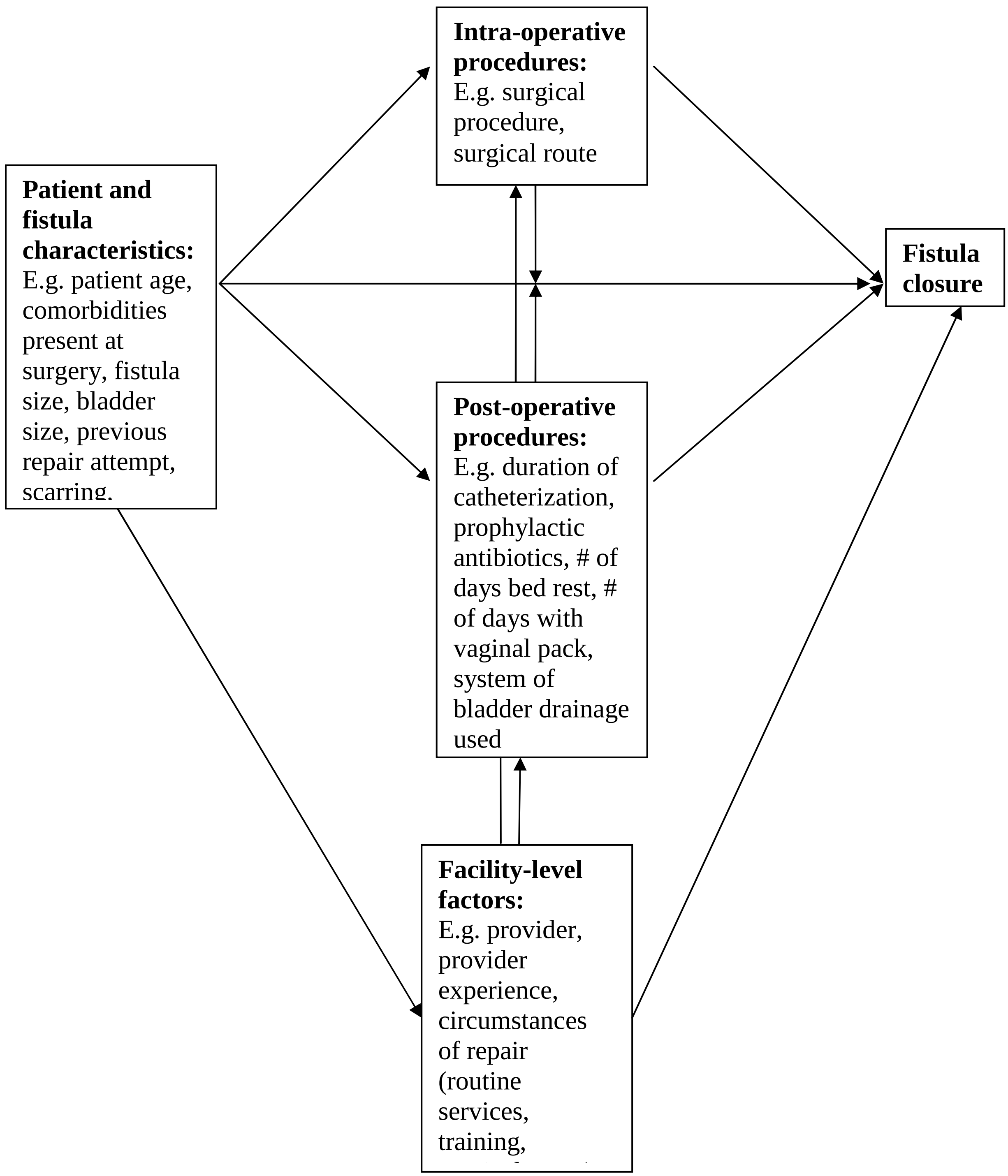
Ethiopia. While the authors suggest that catheterization for 10 days may be sufficient for management of simpler fistulas (and certain types of more complicated fistulas), the conclusions that can be drawn from this study are limited, as the duration of bladder catheterization was not randomized, and may have been influenced by the complexity of the fistula: women catheterized for 10 days were significantly more likely to have an intact urethra ($p=0.009$), smaller size fistula ($p<0.001$), and little or no vaginal scarring ($p<0.001$).[33]

Duration of bladder catheterization has important implications in terms of both cost and hospital-borne infection. Nardos and colleagues illustrate the cost implications of catheterization duration using the example of the Addis Ababa Fistula Hospital, where approximately 1200 fistula repairs are performed annually. Assuming no compromise in patient outcomes, if postoperative hospitalization were to be decreased by four days by removing the bladder catheter at 10 days rather than 14, the number of patients who could receive surgical care could be increased by 20%.[33] Results of a recent Cochrane review of urinary catheter policies following urogenital surgery in adults suggested that shorter-term catheterization was associated with fewer UTIs.[32] Thus, in Chapter 4, I evaluate 1) factors influencing the duration of catheterization and route of repair, 2) the influence of longer duration of catheterization and abdominal route of repair on fistula closure three months following surgery, and 3) whether prognosis of the repair or indication for the procedure moderates the influence of each of these procedures on fistula closure.

Summary and conclusion

While global attention to the issue of vaginal fistula has increased markedly in the past decade, a dearth of research on the topic remains, including research to support the development of a standardized, evidence-based classification system, as well to support effective treatment of the condition. In this dissertation, I review the state of the evidence with regard to patient characteristics, fistula characteristics and peri-operative procedures that influence fistula repair outcomes (Chapter 2). I evaluate the predictive value of five existing classification systems in terms of predicting fistula closure, as well as develop an empirically-derived prognostic score informed by these systems and including factors found to predict fistula repair outcomes in my dataset (Chapter 3). Additionally I evaluate the influence of vaginal (versus abdominal) route of repair, and catheterization duration longer than 14 days, on fistula closure; for these analyses, I explore the role of repair prognosis and indication as both a confounder and effect modifier of these relationships (Chapter 4). Finally I summarize the results, and discuss their implications and future research directions in Chapter 5, the conclusion.

Figure 1.1: Interrelationships between patient and fistula characteristics, intra- and post-operative procedures, and repair outcomes



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Chapter 2 : Factors influencing urinary fistula repair outcomes in developing country settings: a systematic review of the literature

Abstract

The objective of this study was to review and synthesize extant literature examining factors influencing fistula repair outcomes in developing country settings, including fistula and patient characteristics, as well as facility-level factors, such as peri-operative procedures used and other aspects of service delivery. We conducted a systematic review of English and French language literature cited in the Medline database between January 1970 and December 2010, using search terms "obstetric fistula," "vaginal fistula," "urinary bladder fistula," "vesicovaginal fistula" and "fistula." Articles were excluded if they were 1) case reports, cases series or contained 20 or fewer subjects; 2) focused on fistula in industrialized countries; and 3) did not include a statistical analysis of the association between facility or individual-level factors and surgical outcomes. Nineteen articles were included, of which 16 were observational studies. Surgical outcomes included fistula closure, residual incontinence following closure, and closure with no remaining incontinence (dry vs. wet). The presence of scarring and urethral involvement was associated with poor prognosis across the range of outcomes, with some evidence suggesting an association between greater fistula size and smaller bladder size on poor repair prognosis. Evidence regarding the influence of ureteric involvement and prior repair on repair outcomes was insufficient. Results from randomized controlled trials examining prophylactic antibiotic use and repair outcomes were inconclusive, and few observational studies examining peri-operative interventions accounted for confounding of results by fistula severity. We conclude that while a growing number of empirical studies have examined the relationship between surgical outcomes and both patient and fistula characteristics and peri-operative procedures used, there remains a lack of unified, standardized evidence on which to base practice. Further

research is urgently needed to improve the care and treatment of fistula patients in developing countries.

Introduction

Vaginal fistula, or an abnormal opening between the vagina and either the bladder or rectum, is a devastating condition. The immediate consequence is urinary or fecal incontinence, or both. Secondary conditions may include painful rashes resulting from constant leakage of urine, amenorrhea, vaginal stenosis, infertility, bladder stones, and infection.[1] Women suffering from a vaginal fistula often have an odor considered offensive due to the constant leakage of urine and/or feces. As a result, they may be abandoned by their husbands and ostracized by their families and communities. For these reasons, women with this condition have been deemed "the most dispossessed, outcast, powerless group of women in the world."[2] While the number of prevalent cases is unknown, estimates in developing countries have ranged from 654,000[3] to 2 million.[4]

The primary cause of vaginal fistula is prolonged obstructed labor; such fistulas are termed "obstetric fistulas." During prolonged obstructed labor, the fetus's head compresses soft tissues of the bladder, vagina and rectum against the woman's pelvis, cutting off blood supply, causing these tissues to die and slough away. Less frequently, vaginal fistula may result from sexual violence, malignant disease, radiation therapy, or surgical injury (most often to the bladder during hysterectomy or Caesarean section (C-section)). Malignant disease, radiation therapy and surgical injury are the predominant cause of vaginal fistula in industrialized countries; indeed, obstetric fistula does not occur in settings where emergency obstetric care is readily accessible. The injury resulting from obstructed labor is unique in comparison with fistulas resulting from surgical injury: obstructed labor may cause extensive ischemic injury with an area of central necrosis, surrounded by dense scarring, while fistulas resulting from surgical injury are characterized by discrete wounding of otherwise normal tissue.[1]

Treatment of obstetric fistula varies according to how soon a patient presents for care after obstructed labor. Catheterization of women who start leaking after obstructed labor is increasingly used, and cures up to one-fifth of early cases.[5] Unfortunately, most women present months or years after their fistula occurred;[6] surgical closure is then the only option. While the majority (80-95%) of fistulas can be closed surgically,[6] reported success rates range from 56-100%;[7,8] varying by case-mix, number of patients included, and other factors. Up to 33% of women may suffer residual incontinence after successful closure,[9, 10] and an unknown number suffer complications related to intra- and post-operative procedures.

Challenges to providing fistula repair services in developing countries are numerous. Because the vast majority of women with fistula are poor, repair services must be free of charge. Most repairs are conducted within special units (with a dedicated operating theatre and wards) of district hospitals (e.g. primary referral facilities for rural populations) or within specialist fistula centers, and are supported by international donors. Generally, the need for services exceeds available human and infrastructural capacity. In this context, finding ways of providing services in a more cost-effective manner, without compromising surgical outcomes and patients' overall health, is paramount. Despite this need, the current body of published evidence on obstetric fistula has been termed "woefully inadequate by the standards of 21st Century evidence-based medicine."[1]

One priority research need is development of a standardized evidence-based system for classifying fistulas. Currently at least 25 systems are used[11] and parameters measured by these classification systems vary greatly. Early systems described the location of the fistula, while others are more detailed, describing the anatomical structures affected and the extent to which they are affected, as well as factors such as bladder size, fistula size and the amount of scarring involved. To-date, only Goh's and Waaldijk's classification systems have been tested to determine the extent to which their components predict repair outcomes; these analyses were conducted following the adoption of these systems, rather than for the purpose of creating them.[12, 13] In order to develop a single classification system that is prognostic for outcome of repair surgery, it is necessary to determine which fistula characteristics independently predict outcomes, and to identify the minimal parameters required for accurate prognosis, since the simpler a classification system, the more likely it is to be used.

A second research priority is the evaluation of peri-operative techniques and procedures most effective and efficient for fistula repair. Many fistula surgeons have developed their own methods through experience[14] and thus there are a wide variety of pre-, intra- and post-operative procedures/techniques commonly used. For instance, surgeons agree that tissues should be widely mobilized and sutures tension free. However, disagreement remains regarding other interventions such as surgical route, timing of repair, use of interpositional grafts or flaps, and duration of bladder catheterization. Further research to identify optimal interventions would benefit from the availability of a standard system for classifying fistula prognosis, which could be used to adjust for confounding by case-mix and thereby facilitate comparison of results across studies.

In light of the above priorities, we systematically reviewed and synthesized the literature on factors that may influence fistula repair outcomes in developing countries, including fistula and patient characteristics, as well as facility-level factors (e.g. peri-operative procedures and other aspects of service delivery). We then suggest future research priorities in order to fill existing gaps in the literature.

Methods

We conducted a systematic review of the Medline database to identify relevant publications, by searching for articles published from 1970-2010, using the following topic headings: "obstetric fistula," "vaginal fistula," "urinary bladder fistula," "vesicovaginal fistula" and "fistula"; this yielded 6,589 articles. The search was further refined by excluding the MeSH headings "infant,newborn," "male," "kidney transplantation," "adenocarcinoma," "radiotherapy," "penis," "animals," "prostatectomy," "Crohn's Disease" "child, preschool" "radiation injuries," and "kidney diseases," yielding 2,437 articles. We reviewed titles of these articles excluding those clearly not meeting our eligibility criteria (below). This resulted in 526 articles whose abstracts were reviewed to determine eligibility.

Articles included in the final analysis met the following criteria: 1) peer reviewed; 2) original research; 3) focused on predictors of fistula repair outcomes; 4) published after 1970; and 5) written in French or English. Articles were excluded if they 1) were case reports, cases series or contained 20 or fewer subjects; 2) focused on fistula in industrialized countries (since most of these are secondary to surgery or malignancy, and results from such studies may not be generalizable to developing countries where obstetric fistula predominates); and 3) did not statistically analyze associations between facility or individual-level factors and surgical outcomes. Review of references of published papers yielded no additional articles that met the inclusion criteria, nor any articles published prior to 1970 which statistically analyzed factors predicting surgical outcomes. One additional article was identified via an internet search engine (Google). No relevant articles in French were found.

The heterogeneity of exposures and outcomes studied precluded the possibility of combining the results of the studies with meta-analysis. We thus present a descriptive analysis of the articles identified.

Results

Overview of articles identified

Nineteen articles examining predictors of fistula repair surgery outcomes were identified (Table 2.1). Of these, 13 reported results of retrospective record reviews,[15-27] three were prospective studies,[12, 13, 28] and three were randomized controlled trials (RCTs).[29-31] Sample sizes ranged from 34-1045; slightly over half of the articles had samples over 100[13, 15, 16, 18, 20, 24-26, 30, 32] and one-quarter had samples under 50.[21-23, 31] These articles examined a variety of predictors (Table 2.2): seven examined patient or fistula characteristics,[12-13, 15-17, 25, 28] six examined facility-level factors,[18-22, 27, 30] and five examined both patient or fistula characteristics and facility-level factors.[23-26, 31] Three studies were restricted to women undergoing primary repairs.[13, 24, 30]

Definition of “successful repair” varied, with studies defining successful repair as fistula closure, no residual incontinence among those with closed fistula, or no incontinence (i.e. fistula closure and no residual incontinence) (Table 2.2). Among those studies specifying the timing of outcome assessment, almost all assessed associations between predictors and repair outcomes at discharge from the facility (typically 2-3 weeks after surgery). There were three exceptions. Bland and Gelfand assessed outcome at six weeks following surgery,[28] although it was unclear whether this was also the time of discharge. Safan and colleagues[31] and Morhason-Bello and colleagues[27] examined outcome three months following repair. For those studies not specifying timing of outcome assessment[15, 17, 19, 22, 23] we assumed that outcome was assessed around the time of discharge.

We report results of both bivariate and multivariate analyses, since a minority of the observational studies[12, 13, 16, 24-26] accounted for potential confounding with multivariate analysis. However, associations that did not persist after multivariable adjustment are noted when applicable.

The relationship between patient characteristics and surgical outcomes

Socio-demographic characteristics

Patient age was the most common socio-demographic characteristic studied. Six studies examined the association between age at repair and repair outcomes, two of which detected bivariate associations. Browning et al.’s study of 530 women in Ethiopia found that women with residual incontinence after successful closure were younger (22.5 years) than those without (25.9 years; $p<.001$). Similarly, Kirschner and colleagues found that among 926 patients in Nigeria, younger age was significantly associated with any incontinence (risk difference (RD) -1.9, p=0.01).[26] One study examined the association between patient *age at fistula occurrence* and continence. Lewis et al. found that among 435 patients (505 records; some patients had multiple repairs) in Sierra Leone, patient older age at fistula occurrence had a significant (p=.0192) positive association with complete continence, but this did not remain significant in the final multivariate model.[16] Finally, only Kirschner and colleagues examined other socio-demographic characteristics, such as literacy, education and marital status. The only significant difference found in bivariate analysis was across categories of marital status, with women who were abandoned, divorced or separated having the highest proportions of incontinence (45.2%) following repair.[26]

Duration of the fistula

Six studies examined the association between fistula duration and repair outcomes; three found an association. Olusegun and colleagues found a marginally significant association ($\chi 2=7.53$, p=.06) between fistula duration and successful repair (undefined) among 37 patients in Nigeria, but the direction of the trend was not provided.[22] Raassen and colleagues reported that among 581 women repaired in Kenya, Tanzania and Uganda, patients operated within 3 months of fistula development were more likely to achieve fistula closure (93.9% versus 87.0%, respectively); this association did not hold in multivariate analysis.[13] Similarly, Kirschner et al.'s unadjusted analysis found that longer fistula duration was associated with incontinence following the first surgery (RD 24.1 months, p<001).[26] The remaining three studies did not find an association between duration of fistula and fistula closure,[17] complete continence,[23] and incontinence following successful repair.[25]

Fistula etiology

Most studies in our review included predominantly obstetric fistula cases; however, a study by Kriplani and colleagues in India included fistula of differing origins and examined the influence of etiology on repair outcomes among 34 patients. Fistulas resulted from vaginal delivery after prolonged labor (29.4%), cesarean section or post-cesarean hysterectomy (11.7%), surgical errors (32.3%), or other causes (26.3%). No significant difference in complete continence following repair among fistulas of differing origins was found.[23]

Obstetric history

Five studies examined the influence of parity,[16, 23, 25, 26, 31] two examined the effect of mode of delivery,[25, 26] and one examined the duration of labor and place of delivery on repair outcomes.[26] In bivariate analysis, Kirschner et al. found that lower parity and fewer living children were associated with incontinence following first surgery (RD -1.0, p<.001 and RD -1.0, p<.001, respectively);[26] Browning found a similar trend with regard to lower parity and residual incontinence following successful closure, though this relationship was not significant in multivariate analysis.[25] In contrast, Lewis found that if the delivery that caused the fistula was the woman's first pregnancy, it was significantly (p=.0061) associated with continence following repair, but this did not remain significant in the final multivariate model.[16] Browning found that cesarean delivery offered some protection against residual stress incontinence following successful repair in bivariate analysis; this association did not remain significant in multivariate analysis;[25] the second study found no association of mode of delivery with repair outcomes.

Finally, more days in labor (RD 0.40, p=.002) predicted incontinence following first surgery, while place of delivery did not, in Kirschner et al.'s study.[26]

Patient comorbidities

Only one study examined the association between patient comorbidities and fistula repair outcomes. Bland and Gelfand examined the association between urinary bilharziasis due to *Schistosoma haematobium* and fistula closure six weeks post-surgery among 60 patients, with the hypothesis that fibrosis of the bladder wall caused by urinary bilharziasis may complicate closure and healing. Indeed, 70% of those who were *S. haematobium* negative healed successfully, compared to 37.5% of those who were *S. haematobium* positive.[28]

Summary: The role of patient characteristics

The results of the reviewed studies do not suggest an important role of patient characteristics in predicting repair outcome. While several studies found crude associations between younger age at repair and poor repair prognosis, neither this variable nor age at the time of fistula occurrence independently predicted repair prognosis. Similarly, no evidence supported the independent role of parity, duration of leakage, and mode of delivery on repair outcomes. Other factors related to the causative delivery or obstetric history were evaluated by only one study, and analyses were unadjusted.[26] Finally, the only patient comorbidity evaluated was urinary bilharziasis; this was done among a small sample, and only unadjusted associations were assessed.[28]

<u>The relationship between fistula characteristics and surgical outcomes</u>

Tests of existing classification systems

Only two of the existing classification systems have been correlated (post-development) with patient outcomes. Goh and colleagues tested the association of individual parameters included in the Goh classification system (Table 2.3) with both fistula closure and residual incontinence following closure, among 987 women in Ethiopia. In bivariate analysis, women with "special considerations" (e.g. scarring or circumferential fistula) were significantly less likely to have their fistulas closed compared to those without special considerations, but fistula type was not associated with closure; the authors suggest that the latter finding may have been due to the small numbers of failed repairs. No multivariate analyses were conducted to assess independent predictors of closure. In contrast, when the authors examined incontinence following successful closure, multivariate analysis showed that women with Goh Type 1 fistulas were more likely to be continent than women with Type 4, with a trend towards decreasing continence from Type 2 to 4. Women with larger fistulas, and those with any special considerations, were less likely to be continent.[12] Measures of association and 95% confidence intervals were not reported.

Raassen and colleagues applied Waaldijk's classification system (Table 2.3) to 581 fistula patients in Kenya, Tanzania and Uganda. The authors found that fistula type and size did not significantly influence closure, adjusting for age and duration of leakage (measures of association were not presented). In bivariate analysis, women with Waaldijk Type I fistulas (fistulas not involving the closing mechanism) were less likely to develop residual incontinence following repair.[13]

Fistula size

Six studies examined the association between fistula diameter and repair outcomes. As mentioned above, Goh et al. found that women with larger fistulas were less likely to be continent following successful closure, adjusting for location and scarring or other special considerations.[33] Similarly, Browning found that each centimeter increase in diameter increased the odds of residual stress incontinence by 34% (OR 1.34, 95%CI: 1.16-1.56), after adjusting for patient and fistula characteristics.[9] Lewis and colleagues found that women with larger fistulas were significantly more likely to have incontinence after successful repair in bivariate analysis only.[16] While Kriplani and coauthors did not find a statistically significant difference between average fistula size and incontinence following surgery, cases with incontinence had a higher mean fistula volume than cases without (8.1 vs 2.8 square centimeters, p=.009).[23] No other studies found an association between fistula size and repair outcomes.

Bladder size

Two studies examined the association between bladder size and repair outcomes. Nardos and colleagues found that small bladder size independently predicted failure to close the fistula (OR=2.27, 95%CI: 1.36-3.75).[24] Browning found small bladder size to independently predict incontinence following successful closure (OR=4.1, 95%CI: 1.2-13.8).[9]

Vaginal scarring

Each of the six studies examining the specific influence of vaginal scarring on fistula repair outcomes, including Goh's examination of Type 3 fistula[12] discussed above, detected a detrimental effect of scarring on repair outcomes. Nardos and colleagues found severe vaginal scarring to predict failure to close fistula (OR=2.67, 95%CI: 1.36-3.75), adjusting for bladder, fistula and vaginal characteristics and fistula closure techniques,[24] and Holme and colleagues found presence of scarring to be correlated with failure to close the fistula (Spearman r=.412, p<.001).[15] Browning found that women with scarring had 2.4 times the odds of residual stress incontinence following successful closure (95%CI: 1.5-4.0) adjusting for patient and fistula characteristics.[9] In addition, Lewis and colleagues found moderate (OR=2.14, p=.01) and severe (OR=3.07, p<.001) scarring to progressively predict incontinence[16] and Kirschner similarly found that severe scarring predicted incontinence compared to mild and moderate fibrosis (OR 3.21, 95%CI: 2.10-4.89).[26]

Prior fistula repair

Four studies examined the association between prior repair and repair outcomes. Browning found that women having a repeat procedure were more likely to experience residual incontinence than women undergoing primary repair in bivariate analysis (20% versus 10%, p=.006); however, having a repeat procedure did not predict residual incontinence in multivariate analysis.[9] No other studies found an association between prior repair and repair outcomes.

Location

A number of studies have examined the association between fistula location and repair outcomes. As reviewed above, Goh and colleagues found that the greater the distance of fistulas from the urinary meatus, the increased likelihood of continence.[12] Three studies examined the association between fistula location/type and any continence following surgery. Lewis and colleagues found a statistically significant difference between various fistula locations/types (defined as juxta-cervical, juxta-urethral, mid-vaginal, circumferential, secondary, extensive or vesicouterine) and continence; women with mid-vaginal fistulas were more likely to be continent in bivariate analysis.[16] Kirschner and colleagues similarly found that mid-vaginal fistulas were protective of repair failure, with low fistulas (urethrovaginal, circumferential, juxta-urethral, fistula behind the symphysis pubis) and large fistulas (defined as destruction of the entire anterior vagina) significantly associated with incontinence (OR 2.27, 95%CI: 1.37-3.76 and OR 4.63 (95%CI: 2.50-8.57, respectively), adjusting for fistula duration, number of living children and characteristics of the causative delivery.[26] Safan and colleagues found no association between fistula location and continence, where location was defined as urethrovesical, trigonal or supratrigonal.[31]

Urethral involvement

Five studies examined the specific influence of urethral status on repair outcomes. Raassen et al. found that urethral closing mechanism involvement was not associated with fistula closure, adjusting for age and duration of leakage. In bivariate analyses, involvement of the closing mechanism was associated with residual incontinence.[13] Similarly, Browning found that women whose fistulas involved the urethra had 8.4 times the odds of developing urinary incontinence following successful fistula closure (95%CI: 3.9-17.9), adjusting for other patient and fistula characteristics.[9] Nardos et al.'s analysis of 1045 patients found that those with circumferential or urethral fistulas had 1.56 times the odds (95%CI: 0.94-2.59) of failure to close the fistula compared to those without, while women with complete urethral destruction had 2.29 times greater odds (95%CI: 1.06-4.75) of failure to close the fistula.[24] Kirschner and colleagues found a similar dose-response relationship in terms of predicting any incontinence, whereby partial and complete loss of the urethra were associated with 3.58 (95%CI:2.42-5.31) and 8.04

(95%CI:3.18-20.31) times greater odds of incontinence, respectively, adjusting for fistula duration, number of living children and characteristics of the causative delivery.[26] The same authors also examined circumferential fistula (defined as damage to the bladder neck), finding that women with circumferential defect had eight times higher odds of incontinence (OR 8.78, 95%CI: 5.41-14.27) than women whose bladder neck was intact; partial damage to the bladder neck was associated with over twice the odds of incontinence (OR 2.48, 95%CI: 1.67-3.66).[26] Finally, Lewis et al. found only a marginal association (OR 2.41, p=.08) between partial damage to the urethra and any incontinence post-repair, and no association between complete urethral destruction and any incontinence following repair.[16]

Ureteric involvement

Two studies examined ureteric involvement as a predictor of repair outcomes. Raassen et al.[13] and Lewis et al.[16] included ureteric fistulas as categories in omnibus tests of difference in repair outcome by fistula type/location; the specific influence of ureteric involvement was not evaluated in either study, and prevalence of ureteric involvement was low in both (Waaldijk Type 3 fistula represented 4.5% of Raassen's et al.'s sample,[13] and 1% of fistulas in Lewis et al.'s study were ureteric).[16]

Combined vesicovaginal and rectovaginal fistulas and multiple urinary fistulas

Several studies examined the influence of combined VVF/RVF on repair outcomes. Raassen et al. found no difference in fistula closure between those with VVF/RVF and VVF alone.[13] Similarly Browning found that patients with combined fistulas did not have significantly more residual stress incontinence compared to those without RVF.[25] In contrast, Kirschner et al. found that women with combined VVF/RVF had three times the odds of incontinence compared to those without (OR 3.05, 95%CI: 1.65-5.64), adjusting for number of living children and fistula duration.[26] The influence of combined fistulas was evaluated by Lewis et al. in the omnibus test mentioned above; the specific influence of combined VVF/RVF on repair outcomes was not evaluated. Two studies examined the association between multiple urinary fistulas and repair outcomes (residual incontinence after successful closure[9] and any incontinence[26]). Neither found the number of fistulas to significantly predict repair outcomes.

Summary: The role of fistula characteristics

There is relatively strong evidence to support the negative influence of fistula characteristics, particularly vaginal scarring and urethral involvement, on repair outcomes. Each of the studies examining vaginal scarring found an association with repair outcome, including multivariate analyses demonstrating an independent effect of vaginal scarring on closure[24] residual stress incontinence following closure[25] and any incontinence;[26] one study found a dose-response, with higher degree of scarring resulting in greater likelihood of any incontinence.[16] Similarly, four of five large studies found a significant association between increased degrees of urethral involvement and failure to close the fistula,[24] residual incontinence[12, 25] and any incontinence.[26] Evidence to support the role of fistula size and bladder size, while suggestive, was based on fewer studies. Two large studies found that as fistula size increases, the likelihood of continence following fistula closure decreases, after adjusting for other fistula and patient characteristics,[12, 25] though the only study[13] examining the association between fistula diameter and fistula closure found no association. The two studies examining the association between bladder size and repair outcomes found evidence of an independent effect of bladder size on fistula closure[24] and incontinence following closure,[25] with smaller size predicting failure to close the fistula or increased chances of incontinence after successful closure. Finally, evidence was insufficient regarding the role of prior repair, ureteric involvement, combined VVF/RVF or multiple fistulas on repair outcomes.

<u>The relationship between facility-level factors and surgical outcomes</u>

Use of prophylactic antibiotics

Two RCTs have examined prophylactic antibiotic use and repair outcomes. Tomlinson and Thornton, in their study of 79 women in Benin, examined whether intra-operative intravenous ampicillin reduced the failure rate of VVF repair. While the authors hypothesized that reducing surgical wound infections might improve fistula healing, they found a trend towards higher failure to heal and more incontinence in the intervention group (OR 2.1, 95%CI: 0.75-6.1);[29] we understand heal to refer to fistula closure, since the proposed mediating mechanism between antibiotic use and surgical outcome is reduction of surgical wound infection. More recently, Muleta and colleagues examined the effects of either 80 mg Gentamycin IV or extended use of Amoxicillin, Chloramphenicol or Cortimexazole on fistula closure, finding that the single-dose Gentamycin arm trended toward higher closure rates (94% versus 89.4%, p=.04).[30]

Interpositional grafts or flaps

Four studies examined the effects of Martius flap interpositioning, with mixed results.[18] Safan and colleagues' RCT among 38 patients compared fibrin glue versus Martius flap interpositioning for the repair of complicated obstetric fistula, finding no statistically significant difference in the proportion of patients who were continent after 3 months follow-up.[31] Three retrospective studies compared cases where the Martius flap was used to cases where it was not. One study of 46 women found a higher rate of successful closure among those with a Martius flap (95.2%) as compared to those without (72%, p=.038), particularly in recurrent fistulas.[21] In contrast, a study of 440 women found no statistical difference between groups with regard to fistula closure; however, women with a Martius flap were significantly more likely to have residual incontinence.[18] Finally, an analysis of 966 women found no difference in continence status between those receiving and not receiving Martius flap.[26]

Surgical route

Three retrospective studies examined unadjusted associations between surgical route and repair outcomes. Chigbu and colleagues compared abdominal to vaginal routes for repair of juxta-cervical fistulas among 78 women (65.4% of whom were repaired abdominally). They reported successful fistula closure in 84.3% of women repaired abdominally compared to 77.8% of those repaired vaginally; this difference was not statistically significant. All of the failures in the vaginal group were in cases with difficult access and were subsequently repaired abdominally.[19] In contrast, among 28 repairs, Kriplani and colleagues found significantly lower incontinence (7.14%) using the vaginal approach compared to either the abdominal or combined approach (42.8%, p=.05).[23] Finally, Morhason-Bello and colleagues[27] found no statistically significant differences in continence across 71 cases of mid-vaginal fistula (with no fibrosis or evidence of infection, urethral or bladder neck involvement and without more than one previous repair) repaired either abdominally or vaginally; continence rates were 78.3% versus 80.0%, respectively.

Other peri-operative procedures

Three separate retrospective studies examined single- versus double-layer closure, relaxing incision, and duration of bladder catheterization. Nardos et al. (2009) found that single-layer closure was associated with failure to close the fistula among 1045 patients in bivariate analysis. However, the decision to use single-layer closure was influenced by bladder size, and after adjusting for this and other fistula characteristics, single-layer was no worse than double-layer closure.[24] Kirschner and colleagues found that performance of a relaxing incision to improve exposure of the operative field was associated with twice the odds of incontinence at discharge (OR 1.91, 95%CI: 1.25-3.11), adjusting for number of living children, months with fistula, and place of delivery.[26] Finally, a study conducted by Nardos and colleagues among 212 obstetric fistula patients found no difference in the proportion of repair breakdowns between those catheterized for 10, 12, or 14 days.[20]

Summary: The role of facility-level factors

In summary, there is sparse evidence with regard to the effectiveness of peri-operative procedures on repair outcomes. The two RCTs examining antibiotic use[29, 30] had indeterminate findings. The only study[21] finding a positive effect of Martius graft on fistula closure was small and reported only unadjusted associations. While one study found the Martius Flap to be associated with significantly higher risk of residual incontinence after repair,[18] analyses did not account for a range of potentially confounding factors. All three retrospective studies examining route of repair[19, 23, 27] were small, detected varying directions of effect, and reported only unadjusted associations. The only study examining double- versus single-layer closure found no association after adjusting for bladder size, and relaxing incision was found to be associated with incontinence, though analyses did not control for confounding by other fistula characteristics.[26] Finally, one small study found no difference across patients catheterized for durations ranging from 10-14 days.[20] No other peri-operative procedures have been studied, nor have any studies examined the influence of context of repair or provider experience on repair outcomes.

Discussion

Overview of findings

Most studies reviewed were observational, and few conducted analyses that would permit assessment of the independent effects of individual predictors. Patient and fistula characteristics have been most frequently studied, with multiple studies examining the same predictors. Studies of facility-level factors, such as use of antibiotic prophylaxis and duration of post-operative catheterization, have been less frequently replicated.

The results of the reviewed studies do not support an independent role of patient characteristics in predicting repair outcome. While several studies found crude associations between younger age at repair and poor repair prognosis, neither this variable nor age at the time of fistula occurrence independently predicted repair prognosis. Indeed, it is possible that the relationship between patient age (at either time-point) and repair outcomes is mediated by fistula characteristics, since age is related to pelvic size and may thereby influence the degree of damage caused by the obstructed labor, in turn influencing the prognosis of the repair. Evidence supporting the independent role of parity, duration of leakage, and mode of delivery on repair outcomes was similarly insufficient. Finally, Bland and Gelfand's finding regarding the association of *s. haematobium* and failure of healing is plausible given the association of *s. haematobium* with bladder damage, particularly fibrosis and tissue avascularity. Nonetheless, the results were based on a small sample and only crude associations were tested.

Unlike patient characteristics, the weight of evidence indicates that certain fistula characteristics, particularly scarring and urethral involvement, predict poor repair prognosis. These findings are biologically plausible. Extensive scarring not only inhibits access to the fistula, but also requires use of unhealthy tissue to close the defect.[6] Vaginal scarring can also cause the urethra to be held open, preventing it from functioning normally.[25] Similarly, urethral fistula repair is a complex procedure, whereby surviving tissues must be reassembled as a supple functional organ, which acts both as a passageway for urine, and as a "gatekeeper," ensuring that passage of urine occurs at appropriate times. Moreover, an injured, shortened, fibrotic or scarred urethra may be expected to lead to stress incontinence following successful closure.[6]

The relationship between other fistula characteristics and repair outcomes is less clear. There is some evidence that fistula size and bladder size influence repair outcomes. A number of studies examined the association between fistula diameter and repair outcomes. While two large studies found that as fistula size increases, the likelihood of continence following fistula closure decreases,[12, 25] there may be some overlap in the study population in these two studies as they were conducted at the same facility during overlapping time periods. Nonetheless, these findings are not surprising, as it has been suggested that the more extensive dissection which may be required for larger fistulas can in turn cause post-operative scarring around the urethra, holding the urethra open.[25] The results of two studies examining the association between smaller bladder size and failure to close the fistula[24] and incontinence following closure,[25] are also biologically plausible. In the case of bladder size, loss of bladder tissue means the surgeon must try to close large defects in the bladder with only small remnants of (frequently damaged) bladder tissue; the small resulting bladder size may affect its capacity to retain urine. While no studies detected an independent association of prior repair and repair outcomes, prior repair has been correlated with the degree of vaginal scarring.[15] Thus, prior repair may be an indirect cause of negative repair outcomes, via vaginal scarring; this could explain the lack of an independent role of prior repair after adjusting for vaginal scarring, as was found by both Browning[25] and Lewis and colleagues.[16] Additional studies with sample sizes large enough to study relatively rare exposures such as ureteric involvement are needed.

Few studies have examined the role of facility-level factors, such as peri-operative procedures, on repair outcomes, and all but three were observational study designs. The results of both RCTs examining antibiotic use[29, 30] are difficult to interpret. The findings that prophylactic antibiotic use trended towards higher operative failure and more incontinence compared to no antibiotic use are surprising and counter-intuitive, given the expectation that reducing wound infections would promote fistula closure. The results of a recent trial comparing single-dose versus extended antibiotic use demonstrate a marginally significant benefit in favor of single-dose antibiotics, though reasons for such a trend are unclear. However, the confidence intervals for both results were compatible with a chance result. The RCT comparing fibrin glue to Martius flap interpositioning was also inconclusive, due to its small sample size.

Observational studies examining medical interventions are subject to confounding by indication, or prognosis, whereby providers prescribe vigorous therapy when the outlook is poor.[34] This applies to observational studies examining peri-operative interventions related to fistula surgery. For instance, Nardos et al.[20] demonstrated that women catheterized for fewer days were significantly more likely to have fistula characteristics associated with a favorable repair prognosis, including an intact urethra and little or no vaginal scarring; this and the limited power of the study to detect clinically significant differences between catheterization groups limit the conclusions that can be drawn from the study. In contrast, while Kriplani and colleagues[23] found a significantly higher proportion success among fistulas repaired vaginally, analyses did not account for the severity of the fistula, and it is possible that fistulas repaired abdominally may have been more difficult cases. Similarly, while Kirschner and coauthors found that use of relaxing incision was associated with poorer prognosis, analyses did not adjust for scarring and stenosis, factors that the authors acknowledge may have indicated use of relaxing incision.[26]

Several observational studies restricted their samples to women meeting specific characteristics, or conducted stratified analyses. However, this approach does adjust for multiple confounding factors. For instance, while two studies[19, 27] examining route of repair restricted study samples to women with fistulas that can be repaired either abdominally or vaginally (juxta-cervical and mid-vaginal fistulas, respectively), patients repaired abdominally may have exhibited other characteristics associated with both abdominal route and repair outcome. Similarly, while Browning[18] found that a significantly higher proportion of women experienced residual incontinence after repair, analyses stratified by components of the Goh classification system and other subgroups demonstrated that fistulas repaired with Martius flap may have been more difficult cases. While differences persisted within select subgroups (e.g. urethral fistulas), it is not possible to completely exclude the possibility of confounding by indication: for instance, among urethral fistulas, those repaired with Martius flap may have been larger. Further, as acknowledged by the author, since repairs conducted with Martius flap were conducted at an earlier time point in the author's surgical career, results may be confounded by his increased level of experience.[18]

Implications and future directions

Evidence to support existing classification systems

There is wide agreement among those working in the field of fistula care and treatment that a single, evidence-based standardized system of classifying obstetric fistula is needed.[6, 11, 35-37] The development of such a system requires evidence demonstrating which fistula characteristics independently predict outcomes, and identification of the minimal parameters required for accurate prognosis. The studies reviewed above which tested components of the Goh and Waaldijk classification systems to evaluate whether they predict repair outcomes[12, 13] represent useful additions to the evidence-base regarding the relative importance of different fistula characteristics in predicting repair outcomes. However, these studies cannot in and of themselves determine the sufficiency of either system in predicting repair outcomes, nor the superiority of one over another. First, since these systems were not empirically derived, it is possible that other patient or fistula characteristics not included are also important in predicting repair outcomes. Similarly, the inability of any component of these systems to predict fistula closure must not be interpreted to mean that these components or the systems themselves lack prognostic value. Instead, these studies may have been underpowered to detect small differences. For instance, while these studies did not identify any independent predictors of fistula closure, Nardos and coauthors'[24] larger study found that complete urethral destruction and severe vaginal scarring (approximations of parameters included in the Goh system) independently predicted fistula closure.[24] It is also important to note that while the results suggesting aspects of Goh's system predict residual incontinence[12] were replicated by Browning,[25] the additional evidence provided by the latter study is hard to interpret because of the possible overlap in study populations.

Future research priorities

In order to develop a single, standardized prognostic system for classifying fistulas, additional research confirming the prognostic value of parameters included in existing classification systems is needed. In addition, it is necessary to explore if other parameters not included in the current classification systems predict repair outcomes, which may indicate that they should be incorporated into an existing or new system. It is also important to compare existing classification systems to assess the discriminatory value of each as a whole in terms of predicting repair outcomes. If it is determined that one system does indeed have higher discriminatory value, and if the system in question has not yet been validated, the system will need to be tested to ensure that it has both inter-rater and intra-rater reliability. A classification system that is overly complicated or difficult to learn will have limited utility in practice, and is unlikely to be adopted.

More research is required to assess which facility-level factors are associated with repair outcomes. In particular, further research is required on factors such as duration of catheterization and route of repair which may be associated with increased hospital stay and risk of infection. Nardos and colleagues[20] illustrated the cost implications of duration of post-repair catheterization; assuming no compromise in patient outcomes, removing bladder catheters at 10 days rather than 14 would decrease hospitalization by four days, increasing by 20% the number of patients who could receive surgical care. Longer duration of bladder catheterization may also increase risk of UTIs. A recent Cochrane review of urinary catheter policies following urogenital surgery in adults examined seven trials comparing shorter postoperative duration of catheter compared to longer; these trials suggested that shorter-term catheterization was associated with fewer UTIs.[38] Given the potential benefits of short-term catheterization in terms of increasing capacity for treating additional patients and the potential reduced risk of nosocomial infection, further empirical evidence is needed to determine the non-inferiority of short-term catheterization compared to longer-term catheterization. Similarly, the vaginal approach to fistula repair may be associated with less blood loss and pain, fewer complications, and a shorter hospital stay; however, it may also be associated with vaginal shortening and scarring.[11] Further research examining the influence of route of repair on repair outcomes is warranted. A standardized system of classifying fistula prognosis will facilitate the conduct of such studies.

Conclusion

A small, albeit growing, number of empirical studies has examined the relationship between fistula repair outcomes and patient characteristics, fistula characteristics and peri-operative procedures used. Many of the studies we reviewed had relatively small sample sizes and did not use rigorous epidemiologic research methods. This, together with the range of predictors studied and variety of definitions of successful repair used, has resulted in lack of a unified evidence-base on most predictor-repair outcome relationships and thus little evidence on which to base clinical practice. Further research is urgently needed to improve the care and treatment of this most marginalized and neglected group of women.

Table 2.1: Publications examining predictors of fistula repair outcomes in developing country settings

Author, Year	Study Design	Population	Sample size	Outcome definition	Exposures of interest	Analytic approach[i]	Statistically significant predictors of repair outcomes[ii]
Kirschner et al., 2010[26]	Retrospective record review	Patients with vesicovaginal fistula; where unit of analysis was individual patient, analyses were restricted to women undergoing first repair	1084 records from 926 patients	Continence (dry vs wet), assessed at time of discharge	Patient characteristics (age, education, parity, number of living children, literacy, language group and marital status), clinical data (cause of fistula and number of previous surgeries) and surgical data (type/location of fistula, degree of fibrosis, surgical approach, and procedures performed)	Independent sample t-tests and Chi-square tests GEE bivariate and multivariate regression. Multivariate models adjusted for days in labor, number of living children, marital status, months with fistula and place of delivery	Partial loss of the urethra, complete loss of the urethra, partial damage to the bladder neck, circumferential defect, relaxing incision, mixed VVF and RVF repair, severe fibrosis, lower fistula (protective), large fistula (protective)
Muleta et al., 2010[30]	RCT	Patients with obstetric fistula undergoing first repair	722 patients	Fistula closure, assessed after catheter removal and prior to discharge	Single-dose Gentamycin vs. extended (7-day) antibiotic use. Extended antibiotic use included any one or combination of Amoxicillin (500mg IV and oral 6 hourly), chloramphenicol (500 mg IV and oral 6 hourly), or cotrimexazole (800 mg orally every 12 hours)	Chi-square, risk difference	Single-dose Gentamycin significantly associated with fistula closure; confidence interval for risk difference marginally significant

[i] Only the analytic approach for the outcome of interest is reported
[ii] Where bivariate and multivariate analyses were conducted, only multivariate results are reported

Author, Year	Study Design	Population	Sample size	Outcome definition	Exposures of interest	Analytic approach[i]	Statistically significant predictors of repair outcomes[ii]
Nardos et al., 2009[24]	Retrospective record review	Patients with obstetric vesicovaginal fistula undergoing first repairs via vaginal route	1045 patients	Fistula closure[iii], assessed after catheter removal and prior to discharge	Fistula location, number of fistula, extent of urethral intactness, extent of scarring, residual bladder size, repair technique (single vs double layer closure)	Logistic bivariate and multivariate regression	Complete urethral destruction, severe vaginal scarring and small bladder size
Lewis et al. 2009[16]	Retrospective record review	Patients with genitourinary fistula	505 records from 435 patients	Continence (dry vs. wet), assessed via subjective appraisal after catheter removal and prior to discharge	Patient demographics (age), obstetric history (index pregnancy), and fistula parameters (number of prior repairs, fistula type, site and size, degree of fibrosis, and urethral status	Chi-square and Wilcoxon rank sum test; bivariate analyses stratified by primary vs. subsequent repair GEE multivariate regression	Whether the patient presented for the 3-month follow-up appointment, degree of fibrosis surrounding the fistula
Olusegun et al. 2009[22]	Retrospective record review	Patients with vesicovaginal fistula	37 patients	Successful repair (undefined)	Duration of fistula before repair	Chi-square	Duration of fistula (marginally significant)
Safan et al. 2009[31]	RCT	Patients with complicated fistula (defined as recurrence, local moderate to severe fibrosis, fistula location involving the bladder neck, and or size of the fistula being more than 1.5 cm in largest diameter)	38 patients	Continence (dry vs. wet), assessed at three months follow-up	Primary exposures were fibrin glue vs martius flap as interpositioning layer. Also examined parity, patient age, attempts of previous repairs, fistula size, and fistula location	Chi-square or Fisher's Exact tests	None

[iii] Unless otherwise specified, fistula closure was assessed using dye test if the patient reported urine leakage

Author, Year	Study Design	Population	Sample size	Outcome definition	Exposures of interest	Analytic approach[i]	Statistically significant predictors of repair outcomes[ii]
Goh et al. 2008[12]	Prospective	Patients with genitourinary fistula (women with rectovaginal fistula only or no bladder tissue excluded)	987 patients	Fistula closure and residual urinary incontinence following successful closure, assessed after catheter removal and prior to discharge	Components of Goh's classification system: Fistula type (characterized by distance of fistula from external urinary meatus), size, "special considerations" (extent of fibrosis and vaginal length, and special circumstances such as previous repair, ureteric involvement, etc)	Chi-square test and logistic multivariate regression (residual incontinence only)	Closure (bivariate only): "Special considerations" (e.g. scarring and circumferential fistulas) Residual incontinence: Greater distance from external urinary meatus (protective), fistula larger than 1.5 cm, "special considerations"
Morhason-Bello et al. 2008[27]	Retrospective record review	Patients with mid-vaginal fistulas with no fibrosis, evidence of infection, urethral or bladder neck involvement and more than one previous repair attempt	71 patients	Continence three months following surgery	Abdominal versus vaginal route of repair	Fisher's exact test	None
Nardos et al. 2008[20]	Retrospective record review	Patients with obstetric fistula (women with rectovaginal fistula only excluded)	212 patients	Fistula closure and residual incontinence, assessed after catheter removal and prior to discharge (differences at 6-month follow-up not tested)	3 duration of catheterization groups: 10 days (group 1), 12 days (group 2), and 14 days (group 3)	Unspecified (chi-square assumed); bivariate analyses stratified by components of Goh classification system	None

Author, Year	Study Design	Population	Sample size	Outcome definition	Exposures of interest	Analytic approach[i]	Statistically significant predictors of repair outcomes[ii]
Raassen et al. 2008[13]	Prospective	Patients with obstetric fistula undergoing first-time repair	581 patients	Fistula closure assessed via dye test prior to catheter removal (14-21 days following surgery) and residual urinary incontinence following successful closure assessed after catheter removal prior to discharge	Patient characteristics (age and duration of leakage) and components of Waaldijk classification system (type of fistula characterized by extent of involvement of closing mechanism and presence of circumferential defect, exceptional fistulas and size)	Chi-square and Fisher's Exact tests and logistic multivariate regression (closure only)	Closure: none Residual incontinence (bivariate only): lack of involvement of closing mechanism (protective)
Holme et al. 2007[15]	Retrospective record review	Patients with obstetric fistula	259 patients	Closure, not closed, residual incontinence; time period unspecified	Scarring	Spearman correlation	Scarring
Browning 2006[18]	Retrospective record review	Patients with obstetric fistula (women with rectovaginal fistula only excluded)	413 repairs	Fistula closure assessed via dye test prior to catheter removal (14-21 days following surgery) and residual urinary incontinence following successful closure assessed after catheter removal prior to discharge	Martius graft	Fisher's Exact test or Chi-Square with continuity correction; bivariate analyses stratified by components of Goh classification system and other fistula characteristics	Closure: none Residual incontinence: Martius graft (among all fistulas examined together, fistula ≥ 6 cm, Goh's Type 2 fistulas (distal edge 2.5-3.5 cm from external meatus), and urethral fistulas

Author, Year	Study Design	Population	Sample size	Outcome definition	Exposures of interest	Analytic approach[i]	Statistically significant predictors of repair outcomes[ii]
Browning 2006[25]	Retrospective record review	Patients with obstetric fistula (women with breakdown of repair, lack of bladder tissue and rectovaginal fistula only excluded)	481 women	Residual incontinence following fistula closure, assessed following catheter removal and prior to discharge	Urethral involvement, repeat surgery, size of fistula, size of bladder, location of ureter, scarring, flap required, presence of rvf, number of vvf, age, parity, duration labor, time since delivery, diameter of fistula, delivery method and outcome of delivery	T-test, Mann-Whitney U test, and logistic multivariate regression	Urethral involvement, repeat repair, size of fistula, size of bladder, rvf present, younger age, lower parity and c-section delivery (protective)
Chigbu et al. 2006[19]	Retrospective record review	Patients with juxta-cervical vesicovaginal fistula	78 women	Fistula closure, time period of assessment unspecified	Route of repair (vaginal vs. abdominal)	T-tests and Chi-square tests	None
Melah et al. 2006[17]	Retrospective record review	Patients with vesicovaginal fistula	80 women	Fistula closure and residual incontinence following closure; time period of assessment unspecified	Early (less than 3 months) vs. late (after 3 months) closure	Chi-square	None
Kriplani et al. 2005[23]	Retrospective record review	Patients with genital fistula (radiation fistulas excluded)	34 women	Continence following catheter removal	Age, parity, duration of fistula, route of repair, cause of occurrence	Levene's test of equality of variances and Chi-square with Yates correction	Abdominal route of repair and volume of fistula

Author, Year	Study Design	Population	Sample size	Outcome definition	Exposures of interest	Analytic approach[i]	Statistically significant predictors of repair outcomes[ii]
Rangnekar et al. 2000[21]	Retrospective record review	Patients with urinary-vaginal fistulas (excluded fistulas situated high on the posterior wall of the bladder and fistulas greater than 1.5cm in size)	46 women	Fistula closure assessed via dye test prior to catheter removal and residual incontinence following closure, assessed with urodynamic test 3 weeks post-operatively.	Martius flap repair	Fisher's exact test	Martius procedure (protective)
Tomlinson and Thornton 1998[29]	RCT	Patients with obstetric vesico-vaginal fistula	79 women	Fistula closure and continued incontinence (positive pad test) at hospital discharge.	500 mg ampicillin	Mann-Whitney (non-parametric tests)	None
Bland and Gelfand 1970[28]	Prospective	Patients with vesicovaginal fistula	60 women	Closed fistula 6 weeks after repair	Urinary bilharziasis defined by presence of ova on bladder biosopsy or urine examination or rectal snip	Chi square with Yates correction	Presence of urinary bilharziasis

Table 2.2: Predictors studied across the articles reviewed, by outcome[iv]

Predictor	Closure	Residual incontinence	Any incontinence	Not specified
Patient Characteristics				
Comorbidities (*s. haematobium*)	28			
Age at fistula repair	13	25, 13	16, 23, 26, 31	
Age at fistula occurrence			16, 26	
Duration of fistula	17, 13	17, 25,13	23, 26	22
Parity		25	16, 23, 26, 31	
Number living children			26	
Mode of delivery		25	26	
Days in labor			26	
Education			26	
Literacy			26	
Place of delivery			26	
Fistula characteristics				
Etiology			21	
Number of fistulas		25	26	
Fistula size	12, 13	25, 12, 13	16, 23, 26, 31	
Bladder size	24	25		
Bladder neck			26	
Scarring	15, 24, 12	15, 25, 12	16, 26	
Location of the fistula	24, 12	25, 12	16, 26, 31	
Extent of urethral involvement / circumferential fistula	24, 13	13, 25	16, 26	
Ureteric involvement	13	13	16	
Combined vvf/rvf	13	25,13	16, 26	
Previous repair		25	16, 23, 31	
Goh type 3 fistula	12	12		
Facility-level factors				
Surgical route	19		23, 27[v]	
Duration catheterization	20	20		
Single vs. double layer closure	24			
Relaxing incision			26	
Fibrin glue vs. Martius flap/graft			31	
Martius fibrofatty flap/graft	18, 21	25	26	
Antibiotic prophylaxis	30, 29	29		

[iv] Articles indicated by reference number
[v] Outcome examined confirmed via personal communication with primary author

Table 2.3: Waaldijk and Goh fistula classification systems

Classification system	**Type and / or description of fistula**	
Waaldijk 1995[39]	Classification	Size
	Type 1 Not involving the closing mechanism	Small <2
		Medium 2-3
	Type 2 Involves closing mechanism	Large 4-5
	A Without (sub)total urethra involvement	Extensive≥ 6
	B With (sub)total urethra involvement	
	a Without circumferential defect	
	b With circumferential defect	
	Type 3 Ureteric and other exceptional fistula	
Goh 2004[40]	Type: distance from fixed reference point	
	Type 1 Distal edge of the fistula >3.5 cm from external urinary meatus	
	Type 2 Distal edge of the fistula 2.5-3.5 cm from external urinary meatus	
	Type 3 Distal edge of the fistula 1.5-<2.5 cm from external urinary meatus	
	Type 4 Distal edge of the fistula <1.5 cm from external urinary meatus	
	Size: largest diameter in centimetres	
	a Size <1.5 cm in the largest diameter	
	b Size 1.5-3 cm in the largest diameter	
	c Size >3 cm in the largest diameter	
	Special considerations	
	i. None or only mild fibrosis (around fistula and/or vagina) and/or vaginal length >6cm, normal bladder capacity	
	ii. Moderate or severe fibrosis (around fistula and/or vagina) and/or reduced vaginal length and/or bladder capacity	
	iii. Special circumstances, e.g. post-radiation, ureteric involvement, circumferential fistula, previous repair	

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Chapter 3 : Development and test of prognostic scoring systems for surgical urinary fistula closure

Abstract

Although over 25 systems exist for classifying vaginal fistula, no studies have examined the comparative value of different systems in predicting surgery outcomes. We tested the discriminatory value of five existing classification systems - those developed by Lawson, Tafesse, Goh, World Health Organization (WHO) and Waaldijk - to predict fistula closure. We also devised a scoring system using patient comorbidities and fistula characteristics found to independently predict fistula closure. We analyzed data for 1274 women with urinary fistula who presented for repair at 11 study sites in Uganda, Guinea, Niger, Nigeria and Bangladesh and returned for follow-up three months following surgery. Using one-half the sample we created multivariate generalized estimating equation models to derive weighted prognostic scores for variables included in each classification system. Using the second half of the sample and the prognostic scores derived above, we developed Receiver Operating Characteristic curves and calculated areas under the curves (AUCs) and corresponding 95% confidence intervals (CI) for each classification system. The scoring systems representing Tafesse's, Goh's and WHO's classification systems had the highest predictive values: AUC 0.60 (95%CI: 0.55-0.65), AUC 0.62 (95%CI: 0.57- 0.68), and AUC 0.63 (95%CI: 0.57-0.68), respectively, compared to the other existing systems; there was no statistically significant difference in the AUCs of these scores. Our proposed empirically-derived prognostic score combined significant predictors of closure in the above classification systems; this score achieved a similar discriminative ability (AUC 0.62, 95%CI: 0.56-0.67) to the scores representing Tafesse's, Goh's and WHO's systems, and contained only few, non-overlapping, components. Further evaluation of the reliability and

validity of existing classification systems is warranted. Consideration should be given to a prognostic score that is evidence-based, simple and easy to use.

Introduction

While only garnering worldwide attention in the past decade, vaginal fistula, or an abnormal opening between the vagina and bladder or between the vagina and rectum, is an ancient condition. Predominantly caused by obstructed labor (in which case it is referred to as “obstetric fistula”), evidence of the injury was found in the mummified remains of an 11th dynasty pharaoh’s wife, whose reign dated around the year 2050 BCE.[1] From the mid 19th century, when the first surgical techniques for repairing vaginal fistulas were developed, efforts have been made to develop a schema for classifying them.[2] Currently at least 25 such systems exist,[3] and the reliability and validity of the majority of them have not been empirically tested. While there is widespread acknowledgement that a single, standardized classification system is needed,[3-7] there remains disagreement with regard to which fistula characteristics this system should include, and what purposes (e.g. prognostic or descriptive) the classification system should serve.

The purposes of existing systems for classifying vaginal fistula, and their characteristics, vary. These classification systems are used for didactic purposes, as a means of facilitating communication and learning. Such systems are also used for planning and executing fistula repair, including assessing the prognosis of repair, and determining the need for referral. For instance, a classification assigned to a fistula during the initial examination at admission to the facility may be used by the examining surgeon to determine whether the fistula would be most appropriately repaired by a highly experienced fistula surgeon, or whether it would be appropriate for a trainee. The majority of systems classify urinary fistulas, or vaginal fistulas that result in urinary incontinence (as opposed to fistulas resulting in fecal incontinence, or rectovaginal fistulas). However, the components measured by different classification systems vary. Some (particularly older) systems describe the location of the fistula only; examples of these are the systems developed by Sims (1852)[2] and Lawson (1968).[8] Other systems such as those developed by Goh,[9] Tafesse[10] and Waaldijk[11] are more detailed, describing the anatomical structures affected and the extent to which these structures are affected, as well as other factors, such as bladder size, the size of the fistula and the amount of scarring involved. Components of these more detailed systems can be variously combined to allow for a precise description of the fistula. The implicit assumption is that as the type increases by number or letter combination (e.g. Type 2Bb versus Type 2A), the worse the prognostic rating, or "grade." Indeed, two of these systems, those developed by Goh and Waaldijk, have been empirically tested to determine the extent to which parameters included in the systems predict repair outcomes.[12, 13] An additional classification presented by the World Health Organization (WHO) in their manual *Obstetric fistula: Guiding principles for clinical management and programme development*,[14] aims to classify fistula on the degree of difficulty of the repair (simple or complex). However, this system has not been validated, nor (to our knowledge) is it currently used in a clinical setting. No systems currently in use are prognostic scoring systems and none include patient characteristics, including comorbidities.

Importantly, each of these systems were developed using clinical judgment, rather than empirical evidence. Indeed, few studies have examined the ability of individual patient or fistula characteristics to predict fistula repair outcomes,[12, 13, 15-23] and due to the relatively small sample sizes of many of these studies and the variety of definitions of successful repair used, the evidence-base on most predictor-repair outcome relationships remains thin. No study to-date has examined the comparative value of the different classification systems for predicting surgical outcomes.

A standardized evidence-based system of classifying the prognosis of fistula repair surgery would have a number of advantages. First, such a system would facilitate communication and learning across fistula surgeons worldwide. In clinical practice, an evidence-based classification system would assist with the appropriate triage or selection of clients.[5] An evidence-based prognostic *scoring* system in particular would have unique advantages. A scoring system could facilitate surgeons' decisions regarding patient referral, by providing thresholds for what constitutes a "good" or "poor" prognosis. In the research setting, a prognostic score would facilitate the evaluation of surgical success rates across facilities, and the effectiveness of interventions independent of patient or fistula characteristics which may be associated with both the intervention and repair prognosis. Such a score would also facilitate the comparative analysis of studies that examine treatment outcomes. In order to be clinically and analytically useful, such a system must be both simple and sufficient. In clinical practice, a simple and sufficient system will facilitate use and increase accuracy of prognostic prediction. For analytic purposes, a prognostic score should accurately adjust for confounding, decreasing opportunities for residual confounding, yet not over-adjusting, which may unnecessarily increase variance.[24]

Using data collected as part of a multi-country prospective cohort study, we first aimed to test the discriminatory value of five existing vaginal fistula classification systems (Lawson's,[8] Waaldijk's,[11] Tafesse's,[10] Goh's[9] and the system proposed by WHO[14]) with regard to predicting fistula closure, the primary goal of fistula repair surgery. These systems were selected because we were able to measure their components using our study instruments, and are either commonly used in clinical settings (Waaldijk, Goh and Tafesse), or represent a range of detail, from the more sparse and descriptive (the Lawson system) to the more exhaustive (the system presented by the WHO). Further, with the exception of the WHO system, all have been explicitly presumed to have prognostic value. Our secondary aim was to evaluate whether the inclusion of patient characteristics or fistula characteristics not included in other classification systems represents an improvement over existing classification systems in terms of predicting fistula closure. These analyses will thus provide an important contribution to efforts spearheaded by the WHO and other international agencies towards the development and acceptance of a single, standardized, evidence-based fistula classification system.

Methods

Study participants

1389 women presenting for fistula repair services at 11 study sites in Uganda, Guinea, Niger, Nigeria and Bangladesh were enrolled between September 2007 and September 2010. Since our primary outcome was urinary fistula closure, 25 women were excluded because they underwent repair for recto-vaginal repair only; an additional 35 women were excluded because they were either referred to other facilities, did not have surgery for medical/safety reasons, or were treated by catheterization; these women were distributed across all facilities. The majority of those undergoing surgery (95.9%) returned for a follow-up visit; these 1274 women constitute the study sample for these analyses. Most of those not retained (70.4%) came from two sites; women not retained were more likely to be malnourished, anemic, and have a failed repair at discharge (39.4% versus 14.9%). The study received national institutional review board (IRB) approval in Nigeria, Uganda, Guinea, and Niger; local (facility-based) ethical review was conducted at two of three facilities in Bangladesh; one of the three study sites chose not to subject the study protocol to ethical review. All patients provided signed informed consent (if the patient was not literate, consent was indicated via thumbprint).

Study procedures

Prior to surgery, facility staff trained in study procedures and interview techniques interviewed women on their socio-demographic characteristics and obstetric history using standardized study questionnaires. All clinical information was collected by either the attending surgeons or nurses using standardized case report forms; in the case of missing information, facility staff were asked to obtain the information (when available) from the patient's clinical records. Prior to surgery, information was collected on comorbidities and any medical care provided for these comorbidities. At the time of surgery, detailed information was collected about characteristics of the fistula, intra-operative procedures performed and surgical outcomes. Following the surgery but prior to discharge, women were queried about post-operative care provided, and at discharge, information about surgical outcomes was once again collected. Participants were asked to return three months following the surgery, at which point a clinical evaluation was conducted to assess surgical outcomes. Surgical repair protocols, including surgical procedures employed and pre- and post-operative care provided, varied across sites, as per routine practice.

Measures

The primary outcome is urinary fistula closure three months following the surgery, whereby the fistula is characterized dichotomously as either "closed" or "open." The primary mechanism of assessing closure was through a pelvic exam and dye test. For 186 women (14.6% of cases) in which no pelvic exam was conducted, fistula closure was determined using the question "does the client have continuous and uncontrolled leakage of urine," asked of every client at the three-month follow-up visit; this question has been used to differentiate between fistulas and other forms of incontinence, which are unlikely to be continuous and uncontrolled, in household-based Demographic and Health (DHS) surveys.[25] At the two sites where pelvic exams were not routinely conducted at follow-up, any patient complaining of leakage of urine underwent a pelvic exam; since women with continued urinary leakage are eager to report their experiences to the surgeon in order for the condition to be rectified, misclassification of outcomes was unlikely. All cases where the dry test was negative but the patient reported continuous and uncontrolled leakage of urine were verified to exclude the possibility of an unclosed ureteric fistula or otherwise misclassified outcome. In the event that a participant had multiple urinary fistulas (n=74), closure refers to closure of all fistulas. For two women with multiple urinary fistulas, the surgery represented the first of a staged repair, and their fistulas were thus considered "closed" despite continued leakage from the remaining fistulas. We also conducted sensitivity analyses using fistula closure at discharge from the facility (Appendix E); fistula closure at discharge was assessed the same way as closure at follow-up.

In order to compare the predictive value of several existing classification systems, we first transformed these systems into scoring systems. Using data collected as part of our study we created variables representing the components of the four classification systems we aimed to compare. The components of Lawson's classification were measured directly in our dataset, with the exception of "massive combination fistula." Massive combination fistulas were defined by Lawson[8] as those that are juxta-urethral, mid-vaginal and juxta-cervical; these three measures in our dataset were thus combined to create the variable “massive combination fistula.”

In terms of Waaldijk’s classification system, non-involvement of the closing system (Type 1 fistulas) was defined as those fistulas that were either explicitly stated in the study questionnaire to not involve the closing mechanism or did not involve complete destruction of the bladder neck. Type 1 fistulas served as a reference category for the various Type 2 fistula subtypes. Subtype 2A fistulas (“*without* (sub)total urethra involvement”) were equated with an intact or partially damaged urethra in our questionnaire, and subtype 2B fistulas (“*with* (sub)total urethra involvement”) were considered to be urethras that were characterized as completely destroyed in the questionnaire. These Type 2 subtypes were further subdivided into four categories, with Type2Ab and Type2Bb fistulas involving circumferential injury (urethra completely separated from the bladder). We defined Type 3 (“ureteric or other exceptional fistula”) fistulas to include mixed vesicovaginal and rectovaginal fistulas, cervical and ureteric fistulas; urethral fistulas were excluded since the urethral closing mechanism and circumferential fistulas are measured as part of the Type 2 category.

With regard to Tafesse’s classification system, the study questionnaire did not objectively measure bladder length, so it was not possible to create variables exactly representing Tafesse’s categorizations of longitudinal bladder diameter greater than 7 centimeters, 4-7 centimeters and less than 4 centimeters. Instead, we equated bladder diameter less than 7 centimeters with the measured category “small” bladder. Similarly, we considered involvement of less than 50% of the anterior vagina to equate with “minimal” tissue loss, greater than 50% involvement to equate with “moderate” tissue loss, and the category obliterated vagina to equate with either “extensive” tissue loss or obliterated vagina according to response categories in the study questionnaire. Urethral involvement was measured by surgeons' estimates of the length of the urethra, in centimeters, categorized according to Tafesse's specifications.

For Goh's classification system, urethral length in centimeters was used to estimate the location of the distal edge of the urethra relative to the external urinary meatus; urethral length was categorized according to Goh's specifications. Classification subtypes i and ii were operationalized by creating a variable representing the presence of moderate or severe fibrosis and / or a small bladder; no measure of vaginal length or bladder capacity was available. Finally, we created a variable representing the classification subtype "special considerations," which included the presence of ureteric involvement, a circumferential fistula, or previous repair.

In order to measure components of the WHO classification, the number of fistulas was dichotomized as one or greater than one, an indication that the urethra was intact was considered to mean absence of urethral involvement, and mild or greater scarring of the vagina was used to indicate presence of scarring. The WHO system does not allow for a "moderate" degree of tissue loss, so we grouped moderate and minimal tissue loss into a single category as a proxy for minimal tissue loss in the WHO system. Since there is considerable overlap between the WHO categories "site" (vesico-vaginal versus non vesico-vaginal fistulas) and "ureter/bladder involvement" (ureters are inside the bladder versus one or both ureters are draining into the vagina or are at the edge of the fistula), we excluded ureteric fistulas from the WHO category "site" and instead created a new variable "ureter involvement" comprising either ureteric location or drainage of ureters into the vagina or at the edge of the fistula. Urethral fistulas are also excluded from the category "site" since urethral involvement is captured by the component "involvement of the urethra / continence mechanism." Similarly, we did not include the component "circumferential damage" in multivariate analyses, since circumferential injury was included in the variable above.

In order to measure fistula size as characterized in Waaldijk's, Goh's and WHO's system, we categorized this variable in three different ways: we created a categorical variable corresponding to Waaldijk's four categories of size (<2, 2-3, 4-5 and ≥6 centimeters), another representing Goh's three size categories (<1.5, 1.5-3, >3), as well as a dichotomous variable with a cut-off at 4 centimeters, corresponding to the categorization of size in the WHO system. The original components of the classification systems and the way they were operationalized for this analysis are summarized in Appendix C.

Finally, we also evaluated whether other variables measured in our dataset, and not included in existing classification systems, merited inclusion in a revised classification system. In particular, we evaluated individual characteristics including patient age, duration of the fistula, and the presence of comorbidities prior to the surgery. Age and duration of the fistula were measured as continuous variables. Comorbidities assessed included presence of malnutrition (yes versus no, as determined through either a skin fold measurement, body mass index or visual assessment), anemia (yes versus no, as determined through either hemoglobin level, hematocrit or visual assessment), UTI (measured using physician and / or nurse reports of UTI), and parasitic infections, including malaria and helminthiasis (surgeon reports). The variable helminthiasis captured both non-specific reports of helminthiasis, as well as *Schistosoma mansoni*, hookworm, and ascariasis; there were no reports of *Schistosoma haematobium*. We also evaluated the presence of female genital cutting (any versus none). In addition, we examined the distributions of ordinal variables included in existing classification systems to determine whether cut-points should be revised.

Statistical analyses

Comparison of derivation and validation cohorts. A split-sample design was employed, whereby one-half of the sample (the derivation cohort) was used to create the complexity scoring systems, and the second (the validation cohort) was used to test these systems. Pre-operative characteristics of patients in the two cohorts were compared using t-tests for continuous variables and Chi-square tests or Fisher's exact tests (where cell sizes were less than 5) for ordinal or dichotomous variables.

Bivariate analyses. Characteristics of patients whose fistulas were closed at the 3 month follow-up visit were compared to those whose fistulas were not closed using risk ratios (RRs) and corresponding 95% confidence intervals (CIs). Risk ratios and 95% CIs were derived using Generalized Estimating Equations (GEE), using an exchangeable correlation structure with a robust standard error estimator. GEE allows for the combination of the effects of variables at different levels into one model, while accounting for the non-independence of observations within higher level units.[26] We present analyses which account for clustering of patient outcomes by facility, rather than surgeon, since facility is the highest level cluster and therefore should provide unbiased results;[27] however, results accounting for clustering by primary surgeon (defined as attending surgeon, n=51) were similar, and are shown in Appendix D. Risk ratios were generated using the logarithm link function and binomial distribution specification in SAS PROC GENMOD.[28] The multivariate model used to develop an empirically-informed classification system included variables associated with repair failure at a p-value $\leq .20$ in bivariate analysis that were conceptually associated with repair outcome and not highly correlated with other variables. In the event that two candidate variables are highly correlated, the variable with the most clinical significance was selected for inclusion in the model.

Creating classification scoring systems (multivariate analyses). Using the derived cohort, we constructed separate multivariate GEE models for each of the classification systems to be compared. As above, RRs were generated using log-binomial models; in two models where the log-binomial model failed to converge, SAS PROC GENMOD's Poisson regression capability with a log link function and robust variance was used.[29] Each model contained variables from our dataset that closely represented each component of the particular classification system (as described above). In the case of the existing classification systems, variables were included in the multivariate model even if they were not statistically significant predictors of repair outcome in bivariate analyses and were highly inter-correlated. Weighted scores for individual classification system components were derived from adjusted RRs; scores were only assigned to those fistula characteristics significant at p-value<.05. Weights were rounded to the nearest whole number.

Comparing classification system scoring systems. Among the validation cohort, sensitivity (the proportion of true positives) and specificity (the proportion of true negatives) were calculated for each scoring system. Receiver Operating Characteristic (ROC) curves depicting the relationship between the proportion of true-positives and false-positives (i.e. the accuracy of predictions) were drawn for each classification system score. Areas under the ROC curves (AUCs) measured by the C-statistic and 95% confidence intervals were calculated for each curve. Curves for each classification system score were compared visually, and, using methods for paired data, AUCs for each curve were statistically compared by calculating the contrast chi-square and corresponding p-value for the difference between the AUCs. All analyses were done using SAS version 9.2; AUCs were calculated using the %roc macro (SAS Institute, Cary, North Carolina), and ROC curves were constructed using the %rocplot macro.[30]

Results

Comparison of derivation and validation cohorts

There were few statistically significant differences between the derivation and validation cohorts with regard to baseline characteristics and repair outcomes. A smaller proportion of women in the derived cohort had a mixed urinary and recto-vaginal fistula (1.7% versus 4.1%) and had piped water in their residence (20.3% versus 25.0%). The proportion of successful fistula closure at the three-month follow-up visit was similar across both cohorts: 81.5% and 82.0% in the derived and validation cohorts, respectively (Table 3.1).

Development of complexity scores

Results of bivariate and multivariate analyses of existing classification systems are shown in Table 3.2. One component of the Lawson classification system, mid-vaginal location, was found to be significantly protective of failure to close the fistula after adjusting for other components of the Lawson classification system (RR .55, 95%CI: 0.33-0.90). Given the lack of operating points available for the creation of an ROC curve no score was developed to represent the Lawson classification system.

The majority of patients (93%) in our sample fell into Waaldijk's "Type 1" category (fistulas not involving the closing mechanism). Thus, only a small proportion of patients comprised the Type 2Aa, Type2Ab, Type2Ba, Type2Bb categories. Patients with Type 2Aa fistulas (fistulas involving the closing mechanism, none or partial urethral involvement and without circumferential defect) had over twice the risk of not having a closed fistula compared to patients with fistulas that did not involve the closing mechanism (RR 2.70, 95%CI: 1.79-4.08). While representing a very small proportion of the sample, patients with a Type2Bb fistula were over three times more likely to experience failure of fistula closure (RR 3.50, 95%CI: 2.26-5.42) than patients without Type2Bb fistulas.

After adjusting for other components of the Tafesse classification system, Class 3 fistulas (circumferential and *not* previously operated) and Class 4 fistulas (both circumferential *and* previously operated), were significantly more likely to not be successfully closed (RR 1.95, 95%CI: 1.05-3.62 and RR 2.28, 95%CI: 1.27-4.11, respectively). Patients with fistulas involving the urethra but not the middle third had almost twice the risk of failure of fistula closure (RR 1.86, 95%CI: 1.27-2.74), and those with fistulas completely involving the middle third or complete destruction of the urethra had over twice the risk of failure (RR 2.17, 95%CI: 1.10-4.29). Finally, women with extensive tissue damage (RR 1.57, 95%CI: 1.21-2.04) or an obliterated vagina (RR 2.64, 95%CI: 2.17-3.21) had greater risk of repair failure than women with minimal tissue damage.

After adjusting for other components of the Goh classification system, urethral length and scarring independently predicted failure to close the fistula, and were scored. Urethral length 2.5-3.5 centimeters was associated with twice the risk of failure (RR 2.04, 95%CI: 1.60-2.61), with a slightly lower effect for urethras 1.5-2 centimeters long (RR 1.68, 95%CI: 1.07-2.66), and a slightly stronger effect for urethras less than 1.5 centimeters long (RR 2.21, 95%CI: 1.33-3.67). A greater than moderate degree of scarring or a small bladder was associated with almost twice the risk of failure to close the fistula (RR 1.77, 95%CI: 1.19-2.64).

In the model representing WHO's classification system, having greater than one urinary fistula, scarring, involvement of the urethra / continence mechanism, extensive tissue damage and having had a prior repair were all independent predictors of failure to close the fistula. Women with more than one urinary fistula had almost twice the risk of repair failure compared with women with a single fistula (RR 1.96, 95%CI: 1.24-3.06). Patients with involvement of the urethra / continence mechanism had over one and a half times the risk of failure to close the fistula than women without (RR 1.65, 95%CI: 1.28-214). Finally, women with extensive tissue loss had almost twice the risk of experiencing failure to close the fistula compared to women with no or minimal tissue loss (RR 1.72, 95%CI: 1.17- 2.54).

Finally, we developed a new multivariate model, based on factors found to be significant predictors of failure to close the fistula in other classification systems, and other factors not included in other classification systems that were found to predict failure to close the fistula at a p-value less than 0.20 in bivariate analysis (Table 3.3). Due to the high inter-correlation between duration of fistula and prior repair, the inclusion of the latter factor (rather than duration of the fistula) in existing classification systems, and fewer missing observations (three as opposed to 367) we included prior repair rather than duration of fistula repair in our model. Similarly, moderate and extensive tissue loss and moderate and extensive scarring were highly correlated in our dataset; we included “moderate or extensive scarring” in our final model, as it may be more objectively measured than loss of tissue, and unlike tissue loss, has been evaluated in prior studies. We also excluded involvement of the closing mechanism: first, this variable was collinear with the variables partial and complete urethral involvement; secondly, “closing mechanism” is not a commonly used anatomical term, and may be understood as damage to the urethral sphincter, or to the combination of anatomical structures that contribute to continence, including a functioning urethral sphincter, quiescent bladder, and functioning musculofascial supports.[31] Thus, it is possible that some surgeons in our study may not have characterized a woman as having a damaged closing mechanism if the urethral sphincter was intact but other components of the continence mechanism were damaged, leading to an underestimate of this measure. We also excluded helminthiasis, since presence of this comorbidity was elicited through an open-ended question about other comorbidities at baseline, and was only reported in one country. Other variables included in this model were fistula size, the presence of necrotic tissue, lack of visibility of the cervix, bladder size, and the component of Waaldijk’s classification system “ureteric and other exceptional fistulas.” After removing variables that did not retain statistical significance after adjusting for other factors, the final model contained greater than one fistula (RR 2.05, 95%CI: 1.28-3.29), moderate or severe scarring (RR 1.57, 95%CI: 1.12-2.19), partial urethral involvement (RR 1.39, 95%CI: 1.05-1.84), and complete destruction of the urethra or transection / circumferential injury (RR 2.37, 95%CI: 1.80-3.11) (Table 3.4).

Validation and comparison of complexity scores

Based on the above models, and adjusted RRs generated for the individual classification system components, we created a scoring system for each classification system. These scores were applied to the validation cohort in order to plot ROC curves (Figure 3.1) and derive corresponding AUCs (Table 3.5). The Waaldijk classification had a 51% probability of correctly distinguishing patients whose fistula failed to close from those whose fistula were successfully closed (95%CI: 0.49-0.52). The Tafesse, Goh and WHO systems, and the proposed empirically-derived score had similar (p=.47) discriminatory values: AUC 0.60 (95%CI: 0.55-0.65), AUC 0.62 (95%CI: 0.57- 0.68), AUC 0.63 (95%CI: 0.57-0.68), and AUC 0.62 (95%CI: 0.56-0.67), respectively.

Discussion

We transformed four existing classification systems into prognostic scores in order to compare their discriminatory value for fistula prognosis. Few components of the Lawson classification system predicted repair outcomes, suggesting that fistula location alone may have limited prognostic utility. The Waaldijk system fared less well than those of Tafesse, Goh and WHO in terms of predicting fistula closure. However, our ability to test Waaldijk's classification system, and particularly to test the influence of Type 2 fistulas and corresponding subcategories, was limited by the small number of patients meeting the criteria of “closing mechanism involvement.” Indeed, the small proportion of women with involvement of the closing mechanism found in this study is in stark contrast to the majority of patients categorized as having Type 2 fistulas in other studies,[11, 12] and may result from varying definitions of “closing mechanism” across surgeons. However, unlike the study of the Waaldijk classification system conducted by Raassen and colleagues, which found no significant predictors of failure to close the fistula 14 days following surgery,[12] we found that Type2aa and Type2Bb fistulas significantly predicted repair failure.

The scores derived from Tafesse’s, Goh’s and WHO’s classification systems demonstrated stronger discriminatory ability in our dataset, though our analyses indicated potential for simplification. As categorized in the Tafesse classification system, the four “Class” subcomponents imply that the joint effect of prior repair and circumferential injury on repair outcome differs from the independent effects of each of these factors. However, this did not appear to be the case in our dataset: when we tested for evidence of multiplicative interaction the cross-product term for prior repair and circumferential fistula was not significant, and the effect estimate for the variable representing “Class 4” fistulas (the joint effect of both factors) is not consistent with the effect that would be expected if the joint effect of both factors was either super-additive or super-multiplicative. Thus, it may be sufficient to account only for the independent effects of prior repair or circumferential fistula, as is done in the classification system presented by the WHO. Similarly, the Tafesse, Goh and WHO systems have components with potential for overlap. For instance, each includes the presence of a circumferential fistula and urethral involvement as unique components of the system, though circumferential fistulas are a subtype of urethral involvement. Similarly, the WHO classification system component "non-VVF" overlaps with the components measuring urethral involvement and location of the ureters, since the latter are consistent with urethral and ureteric fistulas. The Goh classification includes ureteric involvement as a special consideration, though ureteric fistulas may also be captured as under the "Type 1" component, since they are further than 3.5 centimeters from the external urinary meatus. Such redundancies could be eliminated for the purpose of predicting repair prognosis.

In addition, several components of the above classification systems did not independently predict fistula closure. Ureteric involvement, fistula diameter, and mixed RVF/VVF or cervical fistulas were not statistically significant, and prior repair was only marginally significant. No other studies have evaluated the independent influence of ureteric involvement on repair outcomes. Two studies examining the association between fistula size and fistula closure failed to detect a significant association,[12, 32] and the only study to examine the influence of mixed RVF/VVF on fistula closure similarly found no association.[12] Previous studies have failed to detect an independent association between prior repair and repair outcomes; however these studies examined either residual incontinence following successful repair or any incontinence, rather than fistula closure, as an outcome[17, 19, 21, 22] and thus may not be directly comparable. Similarly, scarring did not achieve statistical significance after controlling for other components of the WHO classification system; this is likely due to the high degree of correlation between scarring and extensive tissue loss, another component of the system, and the fact that the category includes "mild scarring," which may not influence repair outcomes.

Measures of urethral involvement (including circumferential defects) and tissue loss or scarring were independent predictors of failed closure in the Tafesse, Goh and WHO systems. An association between both circumferential fistulas and urethral involvement and fistula closure has been reported in another large study: Nardos and colleagues found that women with circumferential or urethral fistulas had 1.56 times the odds of closure failure (95%CI: 0.94-2.59) compared to those without, and women with complete urethral destruction had 2.29 times the odds (95%CI: 1.06-4.75) of failure to close the fistula compared to those without complete destruction.[20] Similarly, extensive tissue loss predicted failure to close the fistula in both the WHO and Tafesse systems, and the model representing Tafesse's system revealed a dose-response relationship, whereby a higher degree of loss was associated with greater risk of failure. While no other studies have examined the association between tissue loss and repair outcomes, tissue loss leads to scarring, which has been found to be associated with fistula closure in previous studies.[16, 20] Goh's Type ii category, defined here as either moderate or severe scarring or small bladder, similarly predicted failure to close the fistula. The component "greater than one fistula" was unique to WHO's classification system, and was found to be significant after adjusting for other factors in that system. Only one other study has examined the relationship between having multiple fistulas present and fistula closure, and no association was found.[20]

Our empirically-derived prognostic score achieved a discriminatory value similar to the Tafesse, Goh and WHO systems. Our system was informed by these systems; however, it includes fewer components than are included in the existing classification systems evaluated. Moreover, its components are non-overlapping and objectively measured, thereby improving likelihood of inter-observer reliability. For instance, in contrast to the Tafesse and Goh classification systems, which measures both circumferential fistula and urethral involvement, we measured "partial urethral involvement" and "circumferential fistula or complete destruction of the urethra" separately, ensuring no overlap between these components. Similarly, we included measures of the presence of scarring rather than the loss of tissue, since it may be easier to measure presence of a factor than its absence. Finally, it is important to remember that while for comparison purposes it was necessary to transform existing classification systems into scores, no existing classification systems are currently scoring systems. A prognostic score that is simple and easy to recall, such as the one proposed here, can be used in the clinical setting, to assist surgeons in planning a repair and making decisions about patient triage. Such a score can also be used for research purposes, to facilitate the statistical adjustment for confounding by prognosis of repair, and enable comparison of results across intervention studies.

None of the systems evaluated here had high predictive accuracy. The highest AUCs observed in this study ranged from 0.60-0.63; while the discriminatory ability of the systems evaluated is still greater than chance, an AUC greater than 0.70 is typically considered to represent good discriminatory value. The low AUCs in this study indicate that factors in the causal pathway between fistula characteristics and fistula closure, such as surgeon skill or peri-operative procedures used, may be equally or more important in determining fistula closure.

There are some limitations to this study. We tested the extent to which loss-to-follow-up may have biased our results by deriving and testing the same classification systems using fistula closure at discharge from the facility, rather than fistula closure at the 3-month follow up visit (Appendix E). This analysis generated different results than those obtained examining fistula closure at follow-up. Similarly to the results reported above, there was overlap in the confidence intervals across the three AUCs compared. However, the components of existing systems that met criteria for inclusion in a scoring system varied (with neither the Waaldijk nor Goh systems containing sufficient operating points for the construction of an ROC curve), as did the weights assigned to components previously included. Our proposed prognostic score contained one new component (bladder size) and no longer included partial urethral involvement. Nonetheless, it is important to note that prevalence of failure to close the fistula at discharge (15.3%) was lower than at 3-months following surgery (18.4), and therefore these analyses may have had decreased statistical power for detecting small differences. Moreover, overall retention in the study was high, decreasing the chances of biased results, and long-term surgical outcomes may provide better indication of the quality of the repair. Secondly, the measures collected in this study are in some cases approximations of measures included in various classification systems, which may affect our ability to accurately assess the ability of the individual components of these classification systems to predict fistula closure. Nonetheless, we attempted to approximate these measures to the best of our ability. Thirdly, we found that model performance declined in the validation cohort compared to the derived cohort. This may be the result of the relatively small number of failures to close the fistula in the two cohorts, and thus unstable estimates. Finally, unlike the other systems tested, the classification system presented by WHO has not explicitly been stated to have prognostic value (no narrative accompanied the presentation of this system); if this was not the intended purpose of this system, our test of this system's prognostic value would lack construct validity.

This study also has important strengths. It represents the first attempt to empirically evaluate the discriminatory value of existing systems for classifying the prognosis of fistula repair, using data collected from a heterogeneous sample of patients across several countries and multiple study sites. It is also the first attempt to both derive and validate a prognostic score using epidemiological data. To-date only one other scoring system (containing two parameters: degree of scarring and extent of urethral damage[33]) for fistula prognosis has been developed; this score was developed as an informal exercise, and the authors characterize its utility as limited due to small sample size and the limited number of components examined. The current study's large sample size enabled the use of a split-sample design, used to validate the prognostic models on a dataset independent of the one used to create the models, thereby decreasing the likelihood of biased measures of classification system performance.[34] Further, its prospective nature allowed for the assessed of both short-term and long-term repair outcomes.

We have demonstrated that while many of the components comprising existing classification systems predict repair outcomes, existing systems can be considerably simplified for prognostic purposes. Further, we have proposed an empirically-derived prognostic score which combines elements of the two most discriminatory systems into a single simple and more objective measure. These results thus represent an important step towards the development of a single standardized fistula classification system. Further research is warranted to validate our findings among other populations of fistula patients, compare the inter-rater and intra-rater reliability of the above systems, and to evaluate additional classification systems whose components we were not able to measure.

Table 3.1: Comparison of derived and validation cohort on baseline characteristics and repair outcome

	Total N	(%)	Derived cohort N	(%)	Validation cohort N	(%)	
Total	1274	(100)	637	(100)	637	(100)	
Rural residence	1088	(86.1)	546	(86.4)	542	(85.8)	
Mean age	28.2	(11.0)	28.2	(11.1)	28.1	(11.0)	
≥ Primary education	267	(21.0)	120	(18.9)	147	(23.1)	*
Years with fistula	3.3	(5.5)	3.4	(5.6)	3.2	(5.4)	*
Previous repair y/n	294	(23.1)	149	(23.4)	145	(22.9)	
Type of fistula reported							
VVF only	1229	(97.1)	622	(98.3)	607	(95.9)	**
RVF and VVF	37	(2.9)	11	(1.7)	26	(4.1)	
Current marital status							
single	23	(1.8)	10	(1.6)	13	(2.1)	
married / as if married	830	(66.1)	403	(64.4)	427	(67.8)	
widowed	61	(4.9)	34	(5.4)	27	(4.3)	
divorced or separated	341	(27.1)	178	(28.4)	163	(25.9)	
other	1	(0.1)	1	(0.2)	0	(0.0)	
Parity	3.4	(2.9)	3.3	(2.9)	3.4	(2.9)	
Commodities in residence							
piped water	288	(22.7)	129	(20.3)	159	(25.0)	**
flush toilet	46	(3.6)	24	(3.8)	22	(3.5)	
electricity	256	(20.1)	119	(18.7)	137	(21.5)	
radio	881	(69.2)	438	(68.8)	443	(69.5)	
TV	199	(15.7)	94	(14.8)	105	(16.5)	
mobile phone	457	(36.0)	221	(34.7)	236	(37.2)	
land line phone	24	(1.9)	12	(1.9)	12	(1.9)	
refrigerator	49	(3.9)	22	(3.5)	27	(4.2)	
Current ability to meet basic needs							
can easily meet needs	327	(25.8)	153	(24.2)	174	(27.4)	
can somewhat meet needs	660	(52.1)	336	(53.1)	324	(51.0)	
can barely satisfy need	281	(22.2)	144	(22.7)	137	(21.6)	
Closed at discharge	1058	(84.7)	534	(85.6)	524	(84.3)	
Closed at 3 mth visit	1041	(81.6)	519	(81.5)	522	(82.0)	

*p-value <.05
**p-value <.20

Table 3.2: Derivation of scoring systems for existing classification systems

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)[vi]	Score [vii]
Lawson						
	Juxta-urethral	24 (20.5)	105 (20.4)	1.16 (0.85-1.60)	0.95 (0.61-1.46)	-
	Mid-vaginal	20 (17.1)	172 (33.2)	0.57 (0.37-0.89)**	0.55 (0.33-0.90)**	-2
	Juxta-cervical	20 (17.1)	87 (16.9)	0.94 (0.61-1.46)	0.81 (0.56-1.18)	-
	Vault	2 (1.7)	17 (3.3)	0.66 (0.34-1.26)**	0.57 (0.27-1.20)*	-
	Massive combination	2 (1.7)	5 (1.0)	1.78 (0.70-4.45)	--	-
Waaldijk						
	Type 1 Not involving closing mechanism	101 (84.9)	490 (94.8)	Ref	Ref	-
	Type 2 Involves closing mechanism	18 (15.3)	27 (5.2)	2.42 (1.85-3.15)**	Ref	-
	Type 2Aa *Without* (sub)total urethra involvement without circumferential defect	8 (6.8)	9 (1.7)	2.42 (1.48-4.00)**	2.70 (1.79-4.08) **	3
	Type 2Ab *Without* (sub)total urethra involvement with circumferential defect	6 (5.1)	13 (2.5)	1.89 (0.85-4.19)*	1.67 (0.82-3.37)*	-
	Type2Ba *With* (sub)total urethra involvement without circumferential defect	1 (0.9)	3 (0.6)	1.63 (0.71-3.75)	1.69 (0.70-4.08)	-
	Type2Bb *With* (sub)total urethra involvement with circumferential defect	2 (1.7)	1 (0.2)	3.73 (2.77-5.04)**	3.50 (2.26-5.42)**	4
	Type 3 Ureteric and other exceptional fistulas[viii]	39 (33.1)	128 (24.7)	1.41 (0.90-2.21)*	1.31 (0.82-2.12)*	-
	Small <2	27 (23.7)	143 (29.1)	Ref	Ref	-
	Medium 2-3	49 (42.6)	254 (51.7)	0.91 (0.62-1.37)	0.95 (0.65-1.38)	-
	Large 4-5	31 (27.0)	75 (15.3)	1.59 (1.06-2.38)**	1.38 (0.97-1.97)*	-
	Extensive$\geq$ 6	7 (6.1)	22 (4.5)	1.20 (0.54-2.69)	1.17 (0.61-2.23)	-
Tafesse						
	Class 1 Non-circumferential, not previously operated	50 (42.4)	352 (67.8)	Ref	Ref	-
	Class 2 Non-circumferential, previously operated	28 (23.7)	98 (18.9)	1.63(0.97-2.73)**	1. 73 (0.93-3.23)*	-
	Class 3 Circumferential, not previously operated	29 (24.6)	57 (11.0)	2.58 (1.44-4.63)**	1. 95 (1.05-3.62)**	2
	Class 4 Circumferential, previously operated	11 (9.3)	12 (2.3)	3.14 (1.85-5.35)**	2. 28 (1.27-4.11)**	2
	I No urethral involvement (urethral length>4cm)	12 (11.9)	116 (25.4)	Ref	Ref	-
	II Urethra involved but not middle 1/3 (2.7-3.9 cm)	47 (46.5)	182 (39.9)	2.56 (1.39-4.72)**	1.86(1.27-2.74)**	2

[vi] Risk ratios are adjusted for all other components of classification system tested
[vii] Scores were derived by rounding adjusted risk ratio to nearest whole number
[viii] This category includes mixed vesicovaginal and rectovaginal fistula, cervical and ureteric fistula. Urethral fistula are excluded from this category since these are measured by other components, and uniquely rectovaginal fistula are excluded since our analyses examine closure of urinary fistula

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)[vi]	Score[vii]
	III Middle 1/3 partly involved (1.4-2.6 cm)	34 (33.7)	142 (31.1)	2.60 (1.26- 5.36)**	1.35 (0.67-2.72)	-
	IV-V Middle 1/3 completely involved or no urethra[ix]	8 (7.9)	16 (3.5)	4.46 (1.99-9.98)**	2.17 (1.10-4.29)**	2
	b-c Longitudinal diameter of bladder ≤ 7 cm[x]	44 (40.7)	119 (24.4)	1.99 (1.23-3.22) **	1.19 (0.78-1.80)	-
	< 50% of anterior vagina involved	34 (28.8)	292 (56.5)	Ref	Ref	-
	> 50% of the anterior vagina wall involved	53 (44.9)	190 (36.8)	1.56 (0.99-2.48)**	1.57 (1.21-2.04)**	2
	Obliterated vagina	31 (26.3)	36 (7.0)	3.16 (1.99-5.02)**	2.64 (2.17-3.21)**	3
Goh						
	Type 1 Distal edge of the fistula >3.5 cm from external urinary meatus (EUM)	20 (18.3)	165 (32.9)	Ref	Ref	-
	Type 2 Distal edge of the fistula 2.5-3.5 cm from EUM	47 (46.5)	180 (39.5)	2.58 (1.43- 4.65)**	2.04 (1.60-2.61)**	2
	Type 3 Distal edge of the fistula 1.5-<2.5 cm from EUM	27 (26.7)	120 (26.3)	2.43 (1.18- 5.03)**	1.68 (1.07-2.66)**	2
	Type 4 Distal edge of the fistula <1.5 cm from EUM	15 (14.9)	37 (8.1)	4.03 (1.90- 8.57)**	2.21 (1.33-3.67)**	2
	a Size <1.5 cm	21 (18.4)	107 (21.7)	Ref	Ref	-
	b Size 1.5-3 cm	49 (43.0)	273 (55.5)	0.88 (0.57-1.37)	0.74 (0.48-1.12)	-
	c Size >3 cm	44 (38.6)	112 (22.8)	1.58 (0.95-2.64)*	0.91 (0.63-1.33)	-
	i. None or only mild fibrosis, and/or vaginal length >6cm, normal bladder capacity	Ref	Ref	Ref	Ref	-
	ii. Moderate or severe fibrosis, and/or reduced vaginal length and/or bladder capacity	75 (63.6)	216 (41.6)	1.98 (1.22-3.23)**	1.77 (1.19-2.64)**	2
	iii. Special considerations, e.g. post-radiation, ureteric involvement, circumferential fistula, previous repair	73 (61.9)	218 (42.0)	1.83 (1.04-3.21)**	1.49 (0.86-2.57)	-
WHO						
	>1 fistula	16 (13.6)	24 (4.6)	2.12 (1.38-3.26)**	2.13 (1.27-3.56)	2
	Site (mixed vvf rvf or cervical fistula[xi])	8 (6.8)	47 (9.1)	0.74 (0.53-1.04)*	0.83 (0.57-1.21)	-
	Size (diameter ≥4 cm)	38 (33.3)	95 (19.3)	1.66 (1.10-2. 50)**	1.13 (0.85-1.51)	-

[ix] Categories IV (Middle 1/3 completely involved but some urethral tissue remains (urethral length <1.4 cm)) and V (no urethra) were collapsed due to the presence of only 1 woman in the latter category

[x] Categories b (Longitudinal diameter 4-7 cm) and c (Longitudinal diameter <4 cm) collapsed and equated with "small" or "no bladder" in our dataset

[xi] In this category are included mixed vesicovaginal and rectovaginal fistula and cervical fistula. Urethral fistula are excluded from this category since these are measured by the component "involvement of the urethra / continence mechanism." Ureteric fistula are excluded as they are measured through the variable "ureter involvement" and uniquely rectovaginal fistula are excluded since our analyses examine closure of urinary fistula

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)[vi]	Score [vii]
	Involvement of the urethra / continence mechanism	72 (61.0)	192 (37.1)	2.04 (1.52-2.76)**	1.80 (1.28-2.54)**	2
	Scarring	94 (79.7)	386 (74.5)	1.30 (0.94-1.80)*	0.99 (0.66-1.48)	
	Circumferential defect[xii]	40 (33.9)	69 (13.3)	2.32 (1.64-3.30)**		
	Extensive tissue loss	31 (26.3)	35 (6.8)	2.64 (1.83-3.80)**	1.90 (1.38- 2.62)**	2
	Ureter involvement[xiii]	32 (27.4)	87 (16.9)	1.64 (0.97-2.76)*	1.12 (0.73-1.73)	-
	Previous repair	39 (33.1)	110 (21.2)	1.43 (1.01- 2.04)**	1.38 (0.96-1.98)*	

**p-value <.05
*p-value <.20

Table 3.3: Additional variables for consideration in a prognostic classification system

Component	Open N (%)	Closed N (%)	RR (95% CI)
Patient characteristics			
Age > 25	65 (55.1)	241 (46.4)	1.10 (0.77-1.56)
Duration of fistula (average years, sd)	5.5 (8.3)	3.0 (4.7)	1.04(1.03-1.06)**
Comorbidities present at baseline			
Genital cutting	35 (29.7)	99 (19.2)	1.31 (0.88-1.95)
Malnutrition	8 (6.8)	31 (6.0)	1.01 (0.46-2.22)
Anemia	9 (7.6)	36 (6.9)	0.88 (0.62-1.24)
UTI	0 (0.0)	2 (0.4)	-
HIV	0 (0.0)	2 (0.4)	-
Malaria	1 (0.8)	3 (0.6)	0.93 (0.33-2.66)
Helminthiasis	20 (16.9)	54 (10.4)	1.21 (1.10-1.33)**
Fistula characteristics not included in above classification systems			
Necrotic tissue present	16 (13.7)	46 (8.9)	1.33 (0.61-2.86)
No or mild scarring	51 (43.2)	356 (68.7)	Ref
Moderate scarring	43 (36.4)	133 (25.7)	1.74 (1.08-2.82)**
Severe scarring	24 (20.3)	29 (5.6)	3.27 (1.91-5.68)**
No urethral involvement	46 (39.0)	326 (62.9)	Ref
Partial urethral involvement	30 (25.4)	119 (23.0)	1.52 (1.12-2.07)**
Complete destruction or transection / circumferential injury	41 (35.0)	72 (14.0)	2.65 (1.87-3.76)**
Non-vvf (ureteric, urethral, rectovaginal, cervical fistula)	78 (66.7)	266 (51.6)	1.71 (1.19-2.44)**
Cervix not visible	27 (22.9)	79 (15.4)	1.43 (0.89 -2.72)*

**p-value <.05
*p-value <.20

Table 3.4: Proposed fistula prognostic score

Component	ARR (95% CI)	Score
>1 urinary fistula	2.05 (1.28-3.29)	2
Moderate or severe scarring	1.57 (1.12-2.19)	2
Partial urethral involvement	1. 39 (1.05-1.84)	1
Complete destruction or transection / circumferential injury	2.37(1.80-3.11)	2

[xii] This variable was not included in multivariate analysis since circumferential fistulas are a type of urethral involvement, captured by another component of the system
[xiii] This variable is a proxy for the WHO variable “ureters draining into the vagina or at edge of the fistula”: non-specified ureteric involvement was included here to avoid overlap with the variable “non-vvf”

Table 3.5: Performance of selected classification systems

	Derived cohort		Validation cohort	
Scoring system	**Proportion failed closures**	**C-statistic (95%CI)**	**Proportion failed closures**	**C-statistic (95%CI)**
Waaldijk		0.53 (0.51- 0.56)		.51 (0.49-0.53)
0	108/616 (17.53%)		110/616 (17.83%)	
3	8/17 (47.06%)		3/12 (25.00%)	
4	2/3 (66.67%)		2/5 (40.00%)	
Tafesse		0.66 (0.61- 0.71)		.60 (0.55-0.65)
0	16/184 (8.70%)		16/188 (8.51%)	
2	38/253 (15.02%)		47/224 (20.98%)	
3	64/200 (32.00%)		52/225 (23.11%)	
Goh		0.62 (0.57-0.67)		0.62 (0.57- 0.68)
0	14/141 (9.93%)		18/141 (12.77%)	
2	44/275 (16.00%)		33/274 (12.04%)	
4	60/221 (27.15%)		64/222 (28.83%)	
WHO		0.69 (0.64-0.74)		.63 (0.57-0.68)
0	32/337 (9.5%)		44/351 (12.54%)	
2	54/233 (23.18%)		44/215 (20.47%)	
4	32/67 (47.76%)		27/71 (38.03%)	
Proposed		0.70 (0.65-0.75)		.62 (0.56-0.67)
0	23/277 (8. 30%)		32/271 (11.81%)	
1	10/78 (12. 82%)		16177 (20.78%)	
2	29/121 (23.97%)		24/147 (16. 33%)	
3	56/161 (34.78%)		43/142 (30.28%)	

Figure 3.1: ROC curves - derived cohort

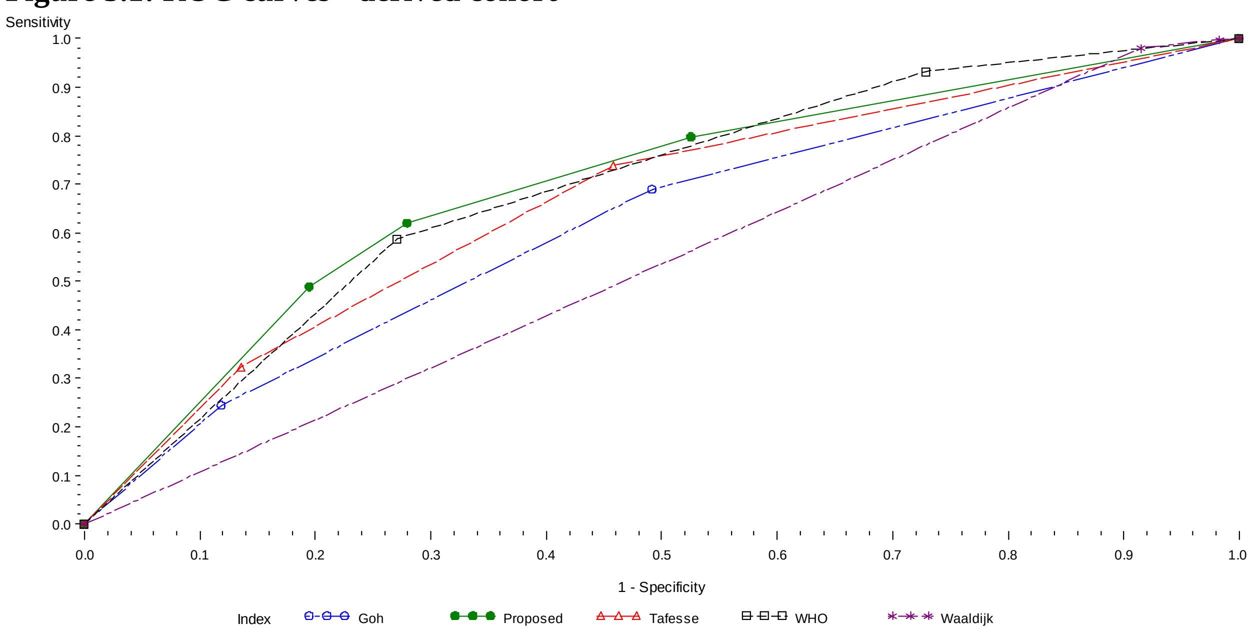
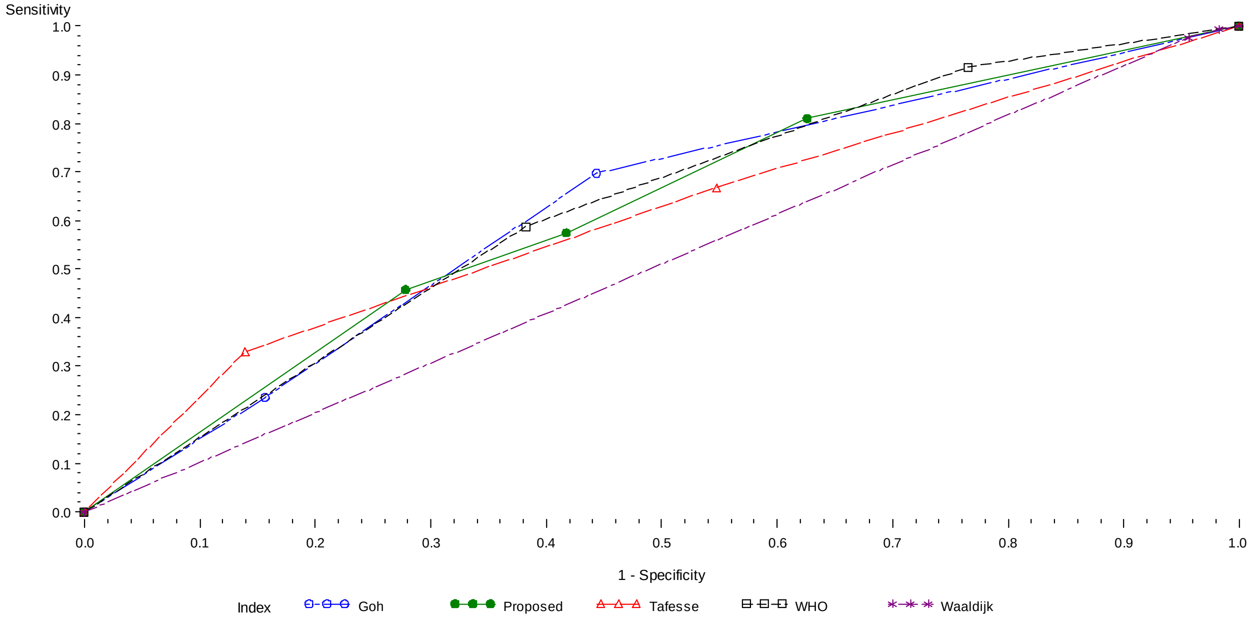


Figure 3.2: ROC curves – validation cohort



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Chapter 4 : The influence of route of repair and duration of catheterization on urinary fistula repair outcomes

Abstract

Few studies have examined the comparative effectiveness of different peri-operative procedures on urinary fistula surgery outcomes. Abdominal (versus vaginal) route of repair and longer duration of catheterization are of particular importance given their potential association with longer-term hospitalization, hospital-associated infection, and increased financial and human resource requirements. Using data collected from 1274 women with urinary fistula who presented for repair at 11 study sites in sub-Saharan Africa and Asia, we used standard multivariable regression and propensity score matching to examine 1) factors influencing route of repair and the duration of catheterization, 2) the influence of route of repair and duration of catheterization on fistula closure three months following surgery independent of indication for repair or repair prognosis, and 3) whether indication for the procedure or fistula prognosis moderates the influence of each of these procedures on repair outcomes. Indication for an abdominal route of repair (limited vaginal access due to extensive scarring or tissue loss, genital infibulation, ureteric involvement, or trigonal, supra-trigonal, vesico-uterine or intracervical location, or other abdominal pathology) was independently associated with abdominal route of repair (adjusted risk ratio (ARR) 13.33, 95%CI: 4.61-38.56); the majority of women undergoing abdominal repair met common indications for such an approach. Each unit increase in prognostic score was associated with 1.07 times higher likelihood of catheterization > 14 days (95%CI: 1.00-1.13), after adjusting for facility, surgeon experience, other fistula characteristics and route of repair. Vaginal route of repair was independently associated with increased risk of failure to close the fistula, relative to abdominal route of repair (ARR 1.42, 95%CI: 1.11-1.81); however, stratified analyses suggested that risk may be elevated among women who meet

common indications for abdominal route of repair. Duration of catheterization > 14 days was associated with failure to close the fistula, after adjusting for severity/repair prognosis and surgeon experience (ARR 1.62, 95%CI: 1.16-2.26); this association persisted in the propensity score-matched sample. Residual confounding by indication and reverse causation cannot be excluded as explanations for this finding.

Introduction

Vaginal fistula is predominantly a childbirth-associated morbidity, whereby the pressure of the fetus's head during obstructed labor creates an abnormal passage between vagina and bladder or between the vagina and rectum, resulting in urinary or fecal incontinence, or both. Fistulas resulting in urinary incontinence are most common, and are often referred to as urinary fistulas. While the majority (80-95%) of urinary fistulas can be closed surgically,[1] the success of repair depends on characteristics and severity of the fistula, surgeon[i] skill, and likely the surgical methods used. Most fistula surgeons have developed their own methods through experience;[2] thus, pre-, intra- and post-operative procedures vary widely across surgeons and facilities. Few studies have examined the comparative effectiveness of different peri-operative interventions related to the surgical management of urinary fistulas.[3-13] Two procedures in particular, abdominal route of repair and extended duration of catheterization following repair, are of critical research interest: each of these procedures is associated with longer-term hospitalization, and therefore a potentially elevated risk of nosocomial infection, particularly urinary tract infection (UTI), and increased financial and human resource requirements.[3]

Recommendations vary with regard to whether a vaginal or abdominal surgical approach should be used for fistula repair. Vaginal approaches are generally thought to be appropriate for any fistula located between the bladder and the vagina,[14, 15] with some full-time fistula surgeons claiming to be able to repair *all* fistulas by the vaginal route.[16] However, abdominal approaches are also often considered to be most appropriate for "complex" fistulas,[17-19] with published indications for an abdominal route of repair including the following: a small capacity or poorly

[i] The term "surgeon" is used here to refer to the individual conducting the surgery, rather than the individual's medical training

compliant bladder which requires bladder augmentation;[15, 17, 18] fistulas involving or close to the ureteric orifice (particularly if ureteric reimplantation is required);[15, 17, 18] vaginal stenosis or other factor inhibiting adequate vaginal exposure of the fistula;[15, 17, 18] size;[18] trigonal or supratrigonal location;[18] intracervical location;[16] and concomitant abdominal pathology.[17] However, the choice of surgical approach remains to some extent a matter of surgeon preference or training,[17, 20] and experience of the surgical team.[18]

Three studies,[5, 9] all retrospective study designs, have examined the association between route of surgery and repair outcomes. Kriplani and colleagues[9] found a significantly higher proportion of success among fistulas repaired vaginally in their sample of 34 women. Chigbu and colleagues,[5] in their sample of 78 women with juxta-cervical fistulas (which can be approached either vaginally and abdominally[5]), found a higher proportion of success among women repaired abdominally (84.3%) compared to vaginally (77.8%); however, this difference was not statistically significant. Finally, Morhason-Bello and colleagues[21] found no statistically significant differences in continence (closed fistula with no residual incontinence) across 71 cases of mid-vaginal fistula (with no fibrosis or evidence of infection, urethral or bladder neck involvement and without more than one previous repair) repaired either abdominally or vaginally; continence rates were 78.3% versus 80.0%, respectively. All three studies were likely underpowered to detect small differences, and examined only unadjusted associations (though the latter two studies restricted the sample by type of fistula). Only Morhason-Bello and colleagues examined indications for vaginal versus abdominal or mixed vaginal and abdominal route of repair, though these were limited due to the strict inclusion criteria employed. No studies have examined the association of route of repair on repair outcomes after adjusting for a range of patient and fistula characteristics.

Similarly, evidence to support the benefit of either short or long-term catheterization following urinary fistula repair surgery is lacking. The bladder is often anecdotally considered to heal better "at rest" (i.e. when it is not filling and emptying),[3, 22] which may justify implementing longer catheterization for cases with worse prognosis. However, the duration of catheterization is informed by convention rather than empirical evidence: no studies have demonstrated the benefit of any duration of catheterization with regard to bladder healing following urinary fistula repair surgery, or indeed, any type of gynecological surgery, and no basic physiologic studies on the dynamics of wound healing in the bladder after fistula repair have been published. In practice, duration of catheterization following pelvic surgery varies widely: a recent survey of 40 fistula surgeons[23] found that catheterization durations ranged from 5 to 21 days. To date, only one study has been published on duration of catheterization following obstetric fistula surgery and repair outcomes;[3] this was a retrospective record review. While the authors found no difference in the proportion of repair breakdown across patients catheterized for 10, 12, and 14 days, the conclusions that can be drawn from this study are limited, as duration was demonstrated to be influenced by severity / complexity of the fistula, only bivariate analyses were conducted, and the study was likely underpowered to detect significant differences.

A shared limitation of the studies examining route of repair and duration of catheterization was the lack of adjustment for the potential imbalance of a range of prognostic features across comparison groups, also termed "confounding by indication." In an observational study, the indication for a treatment may act as a confounder.[24] For instance, a patient's urinary fistula may have certain characteristics which indicate the need for an abdominal route of repair, and these characteristics may also be associated with a poor repair prognosis. Similarly, the severity or prognosis of a patient's condition may lead a medical provider to assign more vigorous therapy (e.g. longer duration of catheterization). Consequently, treatments reserved for those with a poor prognosis will be statistically associated with worse outcomes, even when the treatment itself is beneficial.[25] While observational studies typically rely on methods such as statistical adjustment to minimize differences between comparison groups, such selection bias may be less amenable to standard ways of accounting for confounding.[25] Methods of controlling for non-comparability of comparison groups, such as disease severity scores, may not encompass the totality of factors (including a provider's clinical intuition) that may influence both a provider's decision to administer treatment, as well as eventual repair outcomes. This would result in incomplete adjustment and residual confounding.

Propensity score matching has been proposed as a method particularly suited for the control of confounding by indication. These methods are used to approximate the context of a randomized trial, insofar as treatment groups are comparable on measured confounding factors. Propensity score matching may thus minimize selection bias, since it maximizes the comparability of individuals on a set of observed variables that may influence the provider's decision to administer the treatment.[26] Importantly, however, propensity score matching cannot ensure comparability on unmeasured confounding factors.

Against this background, we used data from a multi-country observational cohort study to elucidate the relationship between route of repair and duration of catheterization on fistula closure. Our first aim was to evaluate which factors predicted both route of repair and duration of catheterization, including the extent to which the choice to undertake these procedures is influenced by either indication for, or prognosis of, repair. Secondly, we aimed to examine the influence of route of repair and duration of catheterization on fistula closure, using both propensity score matching and standard multivariable regression analysis to account for potential confounding. Our third and final aim was to evaluate whether the effect of each of these procedures on fistula closure varied by fistula prognosis or indication.

Methods

Study participants

Between September 2007 and September 2010, 1,389 women presenting for fistula repair services at 11 study sites in Uganda, Guinea, Niger, Nigeria and Bangladesh were enrolled in the study, 1329 of whom underwent urinary fistula repair. Of the women who did not undergo urinary fistula repair, 25 underwent repair for rectovaginal fistula only (and were therefore excluded from these analyses), and 35 women were referred to other facilities, did not have surgery for medical/safety reasons, or were treated by catheterization; these women were evenly distributed across all facilities. Retention was high, with 95.9% of women returning for a follow-up visit; the 1274 women retained constituted the study sample for these analyses. The study received national institutional review board (IRB) approval in Nigeria, Uganda, Guinea, and Niger; local (facility-based) ethical review was conducted at two of three facilities in

Bangladesh.[ii] All patients provided informed consent (consent was signed or indicated via thumbprint if the patient was not literate).

Study procedures

Prior to surgery, women reported on sociodemographic characteristics and obstetric history. Information was also collected on comorbidities and any medical care provided for these comorbidities. At the time of surgery, detailed information was collected about characteristics of the fistula, intra-operative procedures performed and surgical outcomes. Following the surgery but prior to discharge, women were queried about post-operative care provided, and at discharge, information about surgical outcomes was once again collected. Participants were asked to return three months following the surgery, at which point a clinical evaluation was conducted to assess surgical outcomes.

Measures

Aim 1. Our first aim was to evaluate which factors independently predicted both route of repair and duration of catheterization. The primary outcome measures for this aim were surgical route and duration of catheterization. Three possible surgical routes can be used: vaginal, abdominal, or combined. Since we were interested in abdominal route of repair, irrespective of whether it was used in combination with a vaginal approach, this variable was dichotomized as either "abdominal / combined abdominal and vaginal" (hereafter referred to as "abdominal") or "vaginal;" results of analyses excluding those with a combined route of repair are shown in Appendix J. Duration of bladder catheterization was measured by subtracting the recorded date

[ii] The Bangladesh Medical Research Council (BMRC) did not deem it necessary to review the protocol given the study's observational nature. One of three study sites was not interested in subjecting the study protocol to ethical review.

of catheter removal from the date of the surgery; duration of catheterization was first categorized as ≤14 days, 14-21 days, and >21 days. Due to homogenous effects in the two longer duration categories, these categories were collapsed, and we present analyses with catheterization duration categorized dichotomously (≤14 days or >14 days).

The potential predictors of both abdominal route of repair and duration of catheterization included patient characteristics, fistula characteristics, surgeon experience, pre- and intra-operative procedures and site. Patient characteristics assessed included age (reference=25 years or less), years living with the fistula, marital status (currently married versus unmarried), rural residence, education (reference=less than primary education), parity (reference=3 or less) and whether or not the patient had previously undergone surgery for the fistula. Comorbidities assessed included malnutrition (as determined through either skin-fold measurement, body mass index or visual assessment), anemia (as determined through either hemoglobin level, hematocrit or visual assessment), UTI (measured using clinician report), urine-induced contact dermatitis, fever, foot drop, and type of female genital cutting (FGC) present, if any.

Fistula characteristics assessed included bladder size, fistula size, and location. Bladder size was dichotomized as small versus normal or distended (as defined subjectively by the surgeon), and fistula size was dichotomized at 4 centimeters or greater. A composite variable representing ureteric involvement was created, and defined as ureteric or uretero-vaginal location, or if ureters were described to be draining into the vagina or at the edge of the fistula. Urethral involvement was categorized as “partial” (urethra involved but not completely destroyed or transected), and “complete destruction or transection.”

For analyses examining predictors of route of repair only, we evaluated the influence of fistula location in particular on choice of surgical route.   Locations assessed included vesico-uterine, mid-vaginal, juxta-cervical, intra-cervical, trigonal, supra-trigonal, and vault. Based on published indications for abdominal route of repair and factors plausibly indicative of limited vaginal access and significantly associated with abdominal route of repair in our data, we created a composite variable representing "abdominal repair indicated." Specifically, this variable comprised the following indications: presence of extensive scarring or tissue loss, ureteric involvement, trigonal, supra-trigonal, intra-cervical or vesico-uterine location), concomitant abdominal pathology, and female genital infibulation.

For analyses of duration of catheterization only, we examined the influence of fistula repair prognosis, measured using a prognostic score described in detail in Chapter 3. In brief, the score comprises the following variables, all independent predictors of fistula closure: presence of scarring, partial urethral damage, complete urethral damage / transection, and greater than 1 fistula. Each variable / component was assigned a weight, corresponding to its adjusted risk ratio in the final multivariate regression model used to predict fistula closure.   The values of the score range from 0-3, with a higher score representing worse prognosis. In addition, the individual components of the score were also individually assessed.

Surgeon experience was measured by the number of complex repairs the surgeon reported ever conducting; complex was defined subjectively, and the number of such repairs was dichotomized at 200 complex repairs or greater. Variables related to the context of the repair included whether the repair was conducted as part of a training session and whether it was conducted as part of outreach or within a camp. The 11 sites were collapsed into 7 categories to help ensure against sparse cell sizes. Thus, a site in Bangladesh conducting only 5 repairs was combined with another site in the same country which had conducted 48 repairs. Similarly, each of the sites in Niger were combined with sites in Nigeria: site E (n=72) was combined with sites G (n=57) and I (n=151), and site F (n=93) was combined with site H (n=208); this was done because the high collinearity between individual sites and the primary procedures of interest (e.g. no participants at sites E, F, I, and C underwent abdominal route of repair, and no participants at sites E and G were catheterized for 14 days or less) inhibited the estimation of effects for these sites. The remaining 5 sites were examined as individual units.

Aim 2. Our second aim was to examine the influence of route of repair and duration of catheterization on fistula closure. The primary exposure measures for our second aim were route of repair and duration of catheterization, as described above. The primary outcome measure for both analyses was fistula closure three months following the surgery, whereby the fistula was characterized dichotomously as either "closed" or "open." The main mechanism of assessing fistula closure was through a pelvic exam and dye test. For 186 women (14.6% of cases) in which no pelvic exam was conducted, fistula closure was determined using the question "does the client have continuous and uncontrolled leakage of urine," asked of every client at the three-month follow-up visit; this question has been used in household-based Demographic and Health (DHS) surveys[27] to differentiate between fistula and other forms of incontinence, which are unlikely to be continuous and uncontrolled. Outcome misclassification was unlikely, since women with continued urinary leakage are eager to report their experiences to the surgeon in order for the condition to be rectified; further, all cases where the dry test was negative but the patient reported continuous and uncontrolled leakage of urine were verified to exclude the possibility of an unclosed ureteric fistula or other outcome misclassification. At the two sites where pelvic exams were not routinely conducted at follow-up, any patient complaining of leakage of urine underwent a pelvic exam. In the event that a participant had multiple fistulas, closure refers to closure of all fistulas. For two women with multiple fistulas, the surgery represented the first of a staged repair, and their fistulas were thus considered “closed” despite continued leakage from the remaining fistulas.

Potential confounding variables eligible for inclusion in each model were those factors associated with the procedures in question as well as fistula closure. In addition, the propensity score models for duration of catheterization matched participants on intra- and post-operative procedures. Intraoperative procedures included use of Martius flap interpositioning, type of suturing technique (double versus single-layer bladder suture), and route of repair. Post-operative procedures were use of an open versus closed bladder catheter drainage system and post-operative prophylactic antibiotic use.

Aim 3. The third aim assessed whether indication for an abdominal approach is an effect modifier of the relationship between route of repair and fistula closure, and whether repair prognosis modifies the relationship between duration of catheterization and fistula closure; we also show the relationship between route of repair and fistula closure stratified by repair prognosis in Appendix I. For the latter analyses, the prognostic score was dichotomized at a score greater than or equal to 1 (reference=<1); the threshold of 1 was chosen as it neared the optimal threshold based on the balance between true and false positives, as calculated by the Youden Index,[28] (Appendix I) and also represented the median percentile of observations.

All continuous variables that did not have a linear effect with respect to the outcome were categorized in a manner that preserved parsimony and ensured homogeneity across strata; these variables include duration of bladder catheterization, age, parity, fistula size, and provider experience conducting complex repairs, as discussed above.

Statistical analyses

Bivariate analyses. Patient and site-level correlates of route of repair and catheterization duration were compared using t-tests for continuous variables and Chi-square tests or Fisher's exact tests (where cell sizes were less than 5) for ordinal or dichotomous variables. Risk ratios and corresponding 95% confidence intervals (CIs) were generated using the logarithm link function and binomial distribution specification in SAS PROC GENMOD.[29]

Characteristics of patients whose fistulas were closed at the 3 month follow-up visit were compared to those whose fistulas were not closed using risk ratios (RRs) and corresponding 95% confidence intervals (CIs); these were derived using Generalized Estimating Equations (GEE), accounting for clustering of patient outcomes within facilities.

Multivariate analyses. We first assessed independent predictors of abdominal route of repair, and duration of catheterization longer than 14 days, using two separate multivariable models; log-binomial models were once again used to generate RRs. Variables eligible for inclusion in the models were conceptually associated with the procedure and statistically associated (p-value <0.20) with the procedure in bivariate analysis. In the event that variables were too highly correlated only one was included. Thus, parity was measured rather than age, since it could be a measure of care-giving burden (and thus related to length of hospital stay), and malnutrition was included rather than anemia, since it is a cause of the latter. Duration of the fistula and bladder size were excluded because of their collinearity with variables comprising the prognostic score: the prognostic score was chosen over these measures, since information on duration of fistula was missing for almost one-third of participants, and bladder size is only an approximation of bladder capacity, a more accurate measure. Finally, site was measured instead of procedures (with the exception of the variable route of repair in analyses examining predictors of catheterization duration) in multivariate analyses, as we hypothesized that site would better encapsulate unmeasured confounding factors at the site level. Fever and foot drop were not included in the model due to sparse cell sizes.

For our second aim, the evaluation of the independent effect of abdominal route of repair and duration of catheterization on fistula closure at the three-month follow-up visit, we similarly created separate multivariate GEE models for each of these exposures, using the log-binomial specification in GENMOD. Where the log-binomial model failed to converge, SAS PROC GENMOD's Poisson regression capability with a log link function and robust variance was used.[30] These models adjusted for factors conceptually associated with both procedure and outcome, as well as statistically associated (p-value <0.20) with both procedures and outcome in bivariate analysis.

For our third aim, we first created product terms to assess multiplicative interaction between indication for abdominal route of repair and route of repair, and prognosis of the fistula (categorized as a dichotomous variable as well as linearly) and duration of catheterization. However, since the study was likely insufficiently powered to detect the presence of effect modification, we also conducted stratified analyses to visually assess trends in effect sizes across levels of the potential effect modifiers. Analyses of the effect of route of repair on fistula closure were stratified by our measure "abdominal approach indicated," and analyses of the effect of duration of catheterization on fistula closure were stratified by prognostic score (greater than or equal to 1). Bivariate GEE models were used to generate unadjusted RRs and corresponding 95%CIs for these stratified analyses.

Propensity score analysis.

Predicted probabilities (propensity scores) of abdominal route of repair, and catheterization for longer than 14 days, were estimated using two separate multivariable logistic regression models. These propensity score models were developed iteratively, until optimal balance on measured covariates was achieved. For route of repair analyses, the first model included a reduced set of variables: abdominal route of repair indicated, mid-vaginal fistula, juxta-cervical fistula, partial urethral damage and complete urethral damage / transection. The second model included the same measures, in addition to surgeon experience, site, and parity greater than 3. For duration of catheterization greater than 14 days, the first model included a reduced set of variables, including patient and fistula characteristics plausibly associated with surgeon prognostic decision-making (i.e. age, parity, ureteric involvement, bladder size, prognostic score, anemia, footdrop, malnutrition), context of repair (repair conducted as part of training or outreach), as well as intra-operative procedures (use of Martius flap interpositioning,[31] type of suturing technique) and post-operative procedures (open versus closed catheter drainage and whether prophylactic antibiotics were administered). The second expanded model included the above measures as well as site and surgeon experience conducting complex repairs in order to improve balance in covariates across groups.

For duration of catheterization, probabilities of catheterization ≤14 days were calculated to maximize sample size during matching; for route of repair, probabilities of abdominal / mixed vaginal and abdominal repair were calculated. Matching was done using a 1:2 ratio, an optimized matching algorithm and an absolute difference in propensity score of 0.1. Exposed individuals for whom no suitable unexposed match could be found were excluded from the analysis. For analyses of the association between route of repair and fistula closure, 11 participants undergoing abdominal route of repair (19%) were excluded using the reduced propensity score model, and 27 (57%) were excluded with the expanded model. For analyses of the association between duration of catheterization and fistula closure, 119 (31%) participants catheterized for 14 days or less were excluded using the reduced model, and 240 (63%) were excluded with the expanded model. All statistical analyses were conducted using SAS version 9.2, and statistical significance is two-sided at $p < 0.05$ unless stated otherwise.

Results

Sample characteristics

Sample characteristics are shown in Table 4.1. Patients included had a median age of 25 (Interquartile range (IQR) 20-35), and median parity of 2 (IQR 1-5). Over half (65.1%) of the women were currently married, though over a quarter (27.1%, not shown) were divorced or separated from their husbands. The majority of women were from rural areas, and one-fifth had at least a primary education. Almost three quarters of the women with obstetric fistulas had labored at home greater than 24 hours, and over one-third ultimately delivered via cesarean section. The mean number of years women had lived with their fistula was 3.3, and almost one-quarter of the women had previously undergone surgery to repair their fistula. One-fifth of the women presented with signs of FGC, the majority of these were cases were Type II (excision of the clitoris with partial or total removal of labia minora) or III (genital infibulation). The proportion of patients whose fistulas were closed at follow-up was 81.6%.

Predictors of route of repair

Abdominal route of repair was rare, occurring in only 57/1273 (5%) cases; information on route of repair was missing for one study participant. Use of vaginal compared to an abdominal route of repair differed by both facility- and individual-level factors (Table 4.2). Two of the facilities were more likely than the others to use abdominal route of repair, and likelihood of abdominal repair was inversely associated with surgeon experience conducting complex repairs (adjusted risk ratio (ARR) 0.36, 95%CI: 0.13-0.97). Patients undergoing vaginal route of repair were significantly more likely to have a parity of 3 or more (ARR 1.83, 95%CI: 1.03-3.25). Patients with fistulas meeting indications for abdominal repair had a greater than 13-fold risk (ARR 13.33, 95%CI: 4.61-38.56) of having an abdominal repair. Conversely, fistulas that were mid-vaginal were significantly less likely to be repaired abdominally (ARR 0.25, 95%CI: 0.07-0.81), and fistulas involving the urethra were marginally less likely to be repaired abdominally. Having greater than a primary education and a fistula with juxta-cervical location did not independently predict abdominal route of repair.

Predictors of bladder catheterization duration

A minority of women (383/1271, or 30.4%) were catheterized for less than or equal to 14 days; information on catheterization duration was unavailable for 13 participants. The median duration of catheterization in this sample (not shown) was 21 days (IQR 14-27). As with route of repair, duration of catheterization was independently associated with both facility-level factors and fistula characteristics (Table 4.3). Duration of catheterization was significantly influenced by site: only 6 of the 11 sites catheterized women for both less than or equal to 14 days or greater than 14 days, with the remainder of sites (with the exception of 1 site with 5 women) catheterizing women for longer than 14 days (Table 4.3; see Appendix C for the distribution by individual site). Catheterization duration greater than 14 days was also associated with surgeon experience conducting complex repairs (ARR 1.22, 95%CI: 1.00-1.49). Each unit increase in the prognostic score was associated with 1.07 times the risk of long-term catheterization (ARR 1.07, 95% CI: 1.00-1.13). Parity, rural residence, primary education, malnutrition, and vaginal route of repair were not significantly associated with duration of catheterization.

Influence of route of repair on fistula closure

Almost one-fifth (18.8%) of those repaired vaginally experienced repair failure, compared to 10.5% of those repaired abdominally. In bivariate analysis, vaginal route of repair was associated with 1.42 (95%CI: 1.11-1.81) times the risk of failure to close the fistula compared to abdominal route. After adjusting for indication for abdominal route of repair, surgeon experience conducting complex repairs and mid-vaginal location, the risk of vaginal route of repair relative to abdominal route decreased to 1.40 (95%CI: 1.05- 1.87). Product terms for the interaction between vaginal route of repair and indication for abdominal route were not statistically significant. Analyses conducted in the propensity score matched sample, in which propensity scores were created using a reduced set of predictors, found a stronger magnitude of effect compared to the fully adjusted multivariate model; while analyses conducted using the expanded propensity score model found an effect similar to the fully adjusted multivariate model. (Table 4.6) In analyses stratified by indication, among women with fistula meeting indications for abdominal repair, women repaired vaginally had twice the risk of failure compared to those repaired abdominally (RR 1.97, 95%CI: 1.03-3.79); effect estimation among women where an abdominal approach was not indicated was not possible due to sparse cell sizes (no women who underwent abdominal route of repair who did not meet indications for such a repair experienced repair failure). (Table 4.7)

Influence of duration of catheterization on fistula closure

Just over one-fifth (21.4%) of women catheterized for longer than 14 days experienced repair failure, compared to 11.5% of women catheterized for 14 days or less. In bivariate analysis, duration of catheterization for 14 days or longer was associated with a 2-fold increased risk of failure to close the fistula compared to those catheterized for fewer than 14 days (ARR 2.04, 95%CI: 1.16-3.59). This risk decreased after adjusting for fistula prognosis and surgeon experience conducting complex repairs (ARR 1.62, 95%CI: 1.16-2.26) (Table 4.8), with propensity score analysis generating similar results. Product terms for the interaction between catheterization duration and prognostic score were not significant. However, in stratified analysis (Table 4.9), among women with a prognostic score greater than 1, catheterization for 14 days or longer was associated with twice the risk of failure to close the fistula compared to women catheterized for less than 14 days (RR 1.95, 95%CI: 1.19-3.19), while among women with a prognostic score less than or equal to 1, catheterization for 14 days or longer was not significantly associated with risk of failure to close the fistula (RR 1.28, 95%CI: 0.77-2.11).

Discussion

Both route of repair and duration of catheterization were influenced by a combination of patient and fistula characteristics, as well as facility-level factors. Not surprisingly, published indications for abdominal route of repair appeared to influence the decision to undertake an abdominal route of repair, and location of the fistula in an area accessible through the vagina, such as urethral and mid-vaginal location, was protective of an abdominal route of repair. Most women undergoing abdominal repair met the typical indications for an abdominal repair. Those women who did not may have exhibited other unmeasured characteristics which prompted the surgeon to undertake an abdominal repair, or may have been repaired abdominally as a matter of surgeon preference. On the other hand, the vast majority of women who met the indications for an abdominal route of repair were in fact repaired vaginally. Indeed, both site and surgeon experience conducting complex repairs were highly predictive of surgical approach used. It is notable that surgeon experience conducting complex repairs was inversely associated with the decision to undertake an abdominal repair. In a subanalysis (not shown), we evaluated whether more experienced surgeons were less likely to subjectively classify a repair to be “complex,” controlling for fistula prognosis. This did not appear to be the case. Thus, a more likely explanation is that more experienced surgeons are better able to access a range of fistulas vaginally. Finally, parity greater than three was associated with abdominal route of repair. Reasons for this are unclear, though this finding is consistent with Morhason-Bello and colleagues' finding that women repaired abdominally had a significantly higher number of deliveries than those repaired vaginally.[21]

Similar to route of repair, duration of catheterization was influenced by both fistula characteristics as well as facility-level factors. Fistula prognosis independently predicted duration of catheterization after adjusting for other fistula characteristics, surgeon experience, route of repair and site. Thus, it appeared that surgeons were in fact assigning vigorous therapy when a patient's prognostic outlook appeared poor. Our study thus confirms Nardos et al.'s findings that duration of catheterization is influenced by severity of the fistula.[3] However, site was strongly associated with catheterization for longer than 14 days, independent of fistula severity. Therefore, while some sites choose to catheterize women for a specified duration as standard practice, it appears that in sites where duration of catheterization varies, fistula prognosis influences duration of catheterization.

Vaginal route of repair was associated with increased risk of failure to close the fistula, relative to abdominal route of repair, after adjusting for other factors. This finding is surprising, as one might expect that fistulas repaired abdominally would be more complex cases, and therefore have a worse prognosis. Indeed, our results contradict those of Kriplani and colleagues,[9] who found that vaginal route of repair was protective against incontinence (defined as residual incontinence or failure to close the fistula). However, these results must be interpreted with caution. First, it is possible that the types of fistulas that are more likely to be repaired abdominally (i.e. ureteric, trigonal or supratrigonal) are in fact more likely to have a better repair prognosis than fistulas more likely to be repaired vaginally (i.e. urethral fistulas), or that abdominal route of repair is only undertaken for those cases which surgeons deem to be likely to be successfully repaired. Alternatively, it is possible that the abdominal route of repair is in fact beneficial in certain circumstances, such as cases in which the fistula is difficult to access vaginally. Indeed, unadjusted stratified analyses suggested that the risk of failure among women repaired vaginally may be elevated for those women in whom an abdominal repair was indicated compared to those where an abdominal repair was not. However, there were few women who underwent abdominal repair when it was not indicated, resulting in potentially unstable estimates.

The practical implications of a potentially beneficial effect of an abdominal surgical approach are limited. Abdominal approach of repair is primarily performed under general anesthesia; use of general anesthesia requires additional skill on the part of clinicians, is more expensive than the local anesthetics used for a vaginal route of repair,[21] and may not be routinely available in low-resource settings. Moreover, abdominal repairs have been found to be associated with increased blood loss,[18, 21] UTI[21] and longer hospital stay compared to vaginal repairs.[18] This more invasive procedure may also increase risk of surgical site infection, especially in poorly-resourced surgical settings. Further research evaluating which fistula characteristics do in fact indicate the need for an abdominal approach, and the effect of vaginal route of repair across substrata of patients defined by fistula characteristics, is warranted. Any recommendations that women meeting published indications for abdominal repair undergo abdominal route of repair would be premature at this time.

Longer duration of catheterization was independently associated with failure to close the fistula in our study. There are three potential explanations for this finding. The first explanation is that longer term catheterization inhibits bladder healing. A recent study by Boruch and colleagues (2010) evaluating the effects of long-term catheterization on extracellular matrix (ECM) biological scaffold remodeling following partial cystectomy in canines, found that early bladder filling (i.e. shorter duration of catheterization) mediated a constructive remodeling response.[32] While biologic scaffolds composed of ECM are a cutting-edge innovation not feasible for fistula repair in developing countries, the results of this study nonetheless provide some preliminary evidence that removing the catheter early and allowing the bladder to begin filling and emptying, may be beneficial, rather than harmful, to bladder healing. However, an equally plausible explanation is that these results are indicative of residual confounding by indication. We adjusted for fistula characteristics using traditional multivariate techniques as well as through propensity score matching; both methods resulted in a decreased strength of effect of duration of catheterization on repair outcome. Moreover, stratified analyses suggested that risk of failure to close the fistula was particularly elevated among women with a poor prognosis. However, it is possible that there were also unmeasured factors that influenced a surgeon's decision to catheterize a woman for a longer duration of time.

The most likely explanation for our finding that longer-term catheterization predicts failure to close the fistula is that of reverse causation. It is possible that the decision to catheterize a woman for a longer period of time was made upon initial discovery that the fistula was not closed: the catheter may have been left in longer as a final effort to facilitate healing of the fistula. Further research examining the influence of catheterization duration on repair outcomes is warranted; experimental designs that are able to establish temporality and preclude the possibility of confounding by indication would be of particular benefit.

In addition to our inability to exclude reverse causation as an explanation for the association between duration of catheterization and failure to close the fistula, our study has several other limitations. In this multi-country observational study, peri-operative procedures were highly collinear within sites, and varied substantially across sites (Appendix F). In such a context, it is possible that at one or more levels of confounding variables, no one was observed at one or more levels of the exposure;[33] this problem is termed a violation of positivity[34, 35] or “off-support”[36] data. As Oakes and colleagues note, use of regression models in the context of lack of positivity means that comparisons are based on very sparse or model-dependent data; while results from such analyses may be correct, they rely on “heroic modeling assumptions.”[37] Propensity score methods can minimize violations of positivity, in that patients who do not match on probability of exposure are excluded from data analysis. Results obtained using multivariate modeling were similar to those obtained using propensity score matching, increasing our confidence that our findings were not solely based on statistical extrapolation. Another limitation of this study is that the small number of repairs conducted via the abdominal route may have prohibited the detection of small, significant effects. Finally, a related limitation is that we were underpowered to test the presence of effect modification; nonetheless, stratified analyses demonstrated trends in the directions anticipated.

Despite its limitations, this study represents the only comprehensive evaluation of factors that influence the choice of route of repair and duration of catheterization for urinary fistula surgery. It is the largest collection of data assessing predictors of fistula repair outcomes to date, and the only study of this scale to systematically follow women after discharge from the facility in order to determine the long-term effects of the procedures studied on fistula repair outcomes. The provision of fistula care and treatment services in developing countries is fraught with many challenges. In a context which has limited human and infrastructural capacity for meeting high demand for repair services, finding ways of providing services in a cost-effective manner, without compromising surgical outcomes and the overall health of the patient is critical. Additional cohort studies that are adequately powered to test hypotheses of effect modification are warranted to confirm whether abdominal route of repair is indeed beneficial for certain patient populations. A randomized controlled trial assessing the relationship between catheterization and repair outcome would provide evidence with the potential to improve both clinical practice and access to fistula repair services for thousands of women.

Table 4.1: Sample characteristics

Patient characteristics	N (%)
Median parity (IQR)	2 (1-5)
Median age (IQR)	25 (20-35)
Currently married	830 (65.1)
Rural residence	1088 (86.1)
> Primary education	265 (20.8)
Labored at home > 24 hours during causative delivery	614 (72.7)
Delivered via c-section during causative delivery	481 (38.9)
Years with fistula (mean, sd)	3.3 (5.5)
Previously repaired	295 (23.2)
Female genital cutting	
None	1012 (79.6)
Type I[iii]	33 (2.6)
Type II[iv]	124 (9.8)
Type III[v]	97 (7.6)
Other	5 (0.4)
Comorbidities	
Malnutrition	76 (6.0)
Anemia	91 (7.1)
Fever	21 (4.6)
UTI	2 (0.2)
Footdrop	64 (5.0)
Commodities and utilities in household	
Piped water	288 (22.7)
Flush toilet	46 (3.6)
Electricity	256 (20.1)
Radio	881 (69.2)
TV	199 (15.7)
Mobile phone	457 (36.0)
Land line phone	24 (1.9)
Refrigerator	49 (3.9)
Average prognostic score (sd)	1.24 (1.4)
Met indications for abdominal route of repair	400 (31.7)
Surgical approach	
Vaginal	1216 (95.52)
Abdominal	47 (3.69)
Mixed	10 (0.79)
Catheterized ≤ 14 days	383 (30.4%)
Surgical outcomes	
Fistula closed at discharge	1058 (84.7)
Fistula closed at 3 month visit	1039 (81.6)

[iii] Excision of prepuce, with or without excision of clitoris, or part of clitoris
[iv] Excision of the clitoris with partial or total removal of labia minora
[v] Excision of part of all or the external genitalia and narrowing of vaginal opening

Table 4.2: Predictors of vaginal versus abdominal route of repair

	Abdominal / combined N (%)	Vaginal N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[vi]
Total (n=1273)	57	1216		
Patient characteristics at baseline				
Parity > 3	34 (61.8)	410 (34.9)	2.87 (1.68-4.88) **	1.83 (1.03-3.25)**
Age > 25	41 (71.9)	566 (46.5)	2. 81 (1.59-4.96) **	--
Currently married	36 (63.2)	793 (65.2)	0.92 (0.54-1.55)	
Rural residence	52 (91.2)	1035 (85.8)	1.68 (0.68-4.16)	
> Primary education	19 (33.3)	246 (20.3)	1.90 (1.11-3.23) **	1.17 (0.63-2.19)
Average years with fistula (sd)	4.1 (6.5)	3.2 (5.4)	1.02 (0.98-1.07)	
Malnutrition	3 (5.3)	72 (5.9)	0.89 (0.28-2.77)	
Anemia	6 (10.5)	84 (6.9)	1.55 (0.68-3.51)	
Fever	0 (0.0)	20 (4.7)	--	
UTI	0 (0.0)	2 (0.2)	--	
Footdrop	0 (0.0)	64 (5.3)	--	
Female genital infibulation	11 (9.3)	40 (7.8)	2.42 (1.69-3.47)**	
Prior repair	14 (24.6)	281 (23.2)	1.08 (0.60-1.94)	
Fistula characteristics				
Abdominal repair indicated[vii]	52 (91.2)	447 (37.2)	15.76 (2.34-106.06)	13.33 (4.61-38.56)**
Fistula size $\geq$ 4 cm	8 (15.7)	248 (21.3)	0.70 (0.33-1.46)	
Small bladder	12 (23.5)	326 (28.8)	0.77 (0.41-1.45)	
Extensive scarring	2 (3.5)	93 (7.7)	0.45 (0.11-1.82)	
Extensive tissue loss	8 (15.4)	127 (10.5)	1.52 (0.73-3.17)	
Extent of urethral damage				
No damage	48 (87.3)	710 (58.5)	Ref	Ref
Partial damage	3 (5.5)	278 (22.9)	0.17 (0.05-0.55)**	0.40 (0.12-1.36)*
Complete transection or destruction	4 (7.4)	222 (18.4)	0.28 (0.10-0.78)**	0.48 (0.15-1.47)*
Mid-vaginal location	3 (5.4)	366 (30.2)	0.14 (0.04-0.44) **	0.25 (0.07-0.81)**
Trigonal location	6 (10.5)	60 (5.0)	2.13 (0.95-4.79)*	
Supratrigonal location	7 (12.3)	25 (2.1)	5.39 (2.65-10.94)**	
Juxta-cervical location	5 (8.9)	219 (18.2)	0.45 (0.18-1.13)*	0.60 (0.23-1.60)
Intracervical location	7 (12.5)	74 (6.1)	2.08 (0.97-4.45)*	
Vesico-uterine location	10 (17.9)	11 (0.9)	12.85 (7.56-21.84)**	
Vault location	3 (5.3)	32 (2.7)	1.15 (0.29-4.50)	
Ureter involvement	25 (43.9)	183 (15.2)	3.96 (2.40-6.54)**	
Concomitant abdominal pathology	1 (1.8)	1 (0.1)	11.35 (2.77-46.45)**	
Facility level factors / characteristics				

[vi] Each variable for which effect estimates are reported in the column below was adjusted for the other variables for which effect estimates are reported in the column

[vii] Female genital infibulation, extensive scarring, extensive tissue loss, trigonal, supratrigonal, intracervical, vesico-uterine location, ureter involvement or concomitant abdominal pathology

Site				
A (n=70)	9 (12.9)	61 (87.1)	2.61 (1.11-6.16) *	2.02 (0.67-6.11)
B and C (n=53)	2 (4.2)	51 (96.2)	0.77 (0.17-3.39)	0.69 (0.14-3.41)
D (n=246)	8 (3.3)	238 (96.8)	0.66(0.27-1.64)	0.21 (0.07-0.65)**
E, G, and I (n=266)	1 (1.9)	265 (99.6)	0.08 (0.01-0.59) **	0.13 (0.01-1.14)*
F and H (n=276)	1 (0.4)	275 (99.6)	0.07 (0.01-0.57) **	0.18 (0.02-1.57)
J (n=159)	26 (16.4)	133 (83.7)	3.32 (1.65-6.68) **	1.76 (0.66-4.70)
K (n=203)	10 (4.9)	193 (95.1)	Ref	Ref
Surgeon performed over 200 complex repairs	7 (12.3)	404 (35.0)	0.27 (0.12-0.59)**	0.36 (0.13-0.97)**

*p-value<.20

**p-value<.05

Table 4.3: Predictors of catheterization duration < 14 days versus > 14 days

	< 14 days N (%)	> 14 days N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[viii]
Total (n=1261)	383	878		
Patient characteristics at baseline				
Parity > 3	167 (43.6)	275 (31.3)	0.85 (0.79-0.93) **	0.91 (0.78-1.06)
Age > 25	219 (57.2)	383 (43.6)	0.85 (0.79-0.91) **	--
Rural residence	335 (87.5)	742 (84.5)	0.92 (0.84-1.01) *	1.03 (0.84-1.26)
Currently married	256 (66.8)	568 (64.7)	0.97 (0.90-1.05)	
Average years with fistula (sd)	3.9 (5.9)	3.0 (5.2)	0.99 (0.98-1.00) **	--
> Primary education	107 (27.9)	156 (17.8)	0.82 (0.74-0.91) **	0.99 (0.80-1.23)
Anemia	8 (2.1)	81 (9.2)	1.34 (1.24-1.44) **	--
Malnutrition	5 (1.3)	69 (7.9)	1.37 (1.27-1.47) **	1.06 (0.78-1.44)
Fever	2 (1.3)	18 (6.0)	1.38 (1.18-1.62)**	
UTI	1 (0.3)	1 (0.1)	0.72 (0.18-2.87)	
Footdrop	2 (0.5)	61 (6.9)	1.42 (1.34-1.51) **	
Prior repair	81 (21.1)	212 (24.2)	0.88 (0.72-1.09)	
Fistula characteristics				
Ave. prognostic score	1.0 (1.3)	1.4 (1.5)	1.05(1.02-1.08) **	1.07 (1.00-1.13)**
Extent of urethral damage				
No damage	263 (69.2)	488 (55.6)	Ref	
Partial damage	81 (21.3)	199 (22.7)	1.09 (1.00-1.19)*	
Complete transection or destruction	36 (9.5)	187 (21.4)	1.28 (1.19-1.38)**	
> 1 fistula	22 (5.8)	52 (5.9)	1.00 (0.86-1.16)	
Moderate or extensive scarring	129 (33.7)	335 (38.2)	1.07 (0.99-1.14)*	
Small bladder	50 (13.6)	283 (35.1)	1.37 (1.28-1.46) **	--
Ureteric involvement	55 (14.4)	170 (19.5)	1.11 (1.02-1.20) **	1.15 (0.95-1.40)*
Facility level factors / characteristics				
Site				
A (n=68)	6 (8.8)	62 (91.2)	1.76 (1.51-2.05) **	1.98 (1.34-2.94)**
B and C (n=52)	32 (61.5)	20 (38.5)	0.74 (0.51-1.08)	0.76 (0.47-1.23)
D (n=246)	120 (48.8)	126 (51.2)	0.99 (0.83-1.19)	1.01 (0.73-1.40)
E, G, and I (n=263)	1 (0.4)	262 (99.6)	1.92 (1.69-2.20) **	2.10 (1.57-2.81)**
F and H (n=271)	46 (17.8)	225 (83.0)	1.61 (1.39-1.85) **	1.51 (1.15-2.00)**
J (n=158)	80 (50.6)	78 (49.3)	0.95 (0.78-1.17)	1.07 (0.77-1.49)
K (n=203)	98 (48.3)	105 (51.7)	Ref	Ref
Surgeon performed over 200 complex repairs	90 (24.5)	314 (37.8)	1.19 (1.11-1.28)**	1.22 (1.00-1.49)**
Vaginal route of repair	353 (92.2)	850 (96.9)	1.49 (1.13-1.97) **	1.25 (0.83-1.88)
2-layer bladder suture	161 (44.1)	252 (29.7)	0.82 (0.75-0.89) **	--
Martius graft	3 (0.8)	40 (4.7)	1.35 (1.23-1.47) **	--
Open catheter drainage	220 (57.6)	662 (75.9)	1.33 (1.21-1.47)**	--
Post-op drinking regimen	333 (86.9)	778 (88.8)	1.07 (0.95-1.22)	
Prophylactic antibiotics	312 (81.5)	767 (87.5)	1.18 (1.04-1.34)**	--

*p-value<.20
**p-value<.05

[viii] Each variable for which effect estimates are reported in the column below was adjusted for the other variables for which effect estimates are reported in the column

Table 4.4: Patient and fistula characteristics by repair outcome

Characteristics	Open N (%)	Closed N (%)	Unadjusted RR (95% CI)
Total (n=1274)	233	1041	
Patient characteristics			
Age > 25	129 (55.4)	479 (46.0)	1.07 (0.90-1.26)
Duration of fistula (average years, sd)	4.7 (7.3)	3.0 (5.0)	1.03 (1.01-1.04)**
Greater than high school education	27 (11.7)	238 (22.9)	0.81 (0.60-1.08)*
Rural residence	199 (86.1)	889 (86.1)	1.10 (0.84-1.43)
Parity > 3	83 (37.1)	362 (35.9)	0.92 (0.78-1.09)
Delivered via c-section	91 (40.4)	390 (38.5)	1.22 (0.84-1.77)
Prior repair	83 (35.8)	212 (20.4)	1.53 (1.23- 1.90)**
Currently married	141 (60.5)	689 (66.2)	0.81 (0.63-1.05)*
Patient comorbidities			
Female genital cutting	65 (27.9)	194 (18.7)	1.19 (0.89- 1.58)
Malnutrition	18 (7.7)	58 (5.6)	1.23 (0.66- 2.28)
Anemia	19 (8.2)	72 (6.9)	0.99 (0.79-1.23)
UTI	0 (0.0)	2 (0.2)	-
HIV	0 (0.0)	4 (0.4)	-
Malaria	2 (0.9)	4 (0.4)	1.26 (0.87-1.81)
Fistula characteristics			
Average prognostic score	2.1 (1.7)	1.1 (1.3)	1.38 (1.16-1.65)**
Abdominal route of repair indicated	104 (45.0)	296 (28.8)	1.64 (1.28-2.10)**
Juxta-urethral	46 (19.8)	230 (22.2)	0.99 (0.77-1.27)
Mid-vaginal	49 (21.2)	320 (30.9)	0.74 (0.56-0.99)*
Juxta-cervical	38 (16.5)	187 (18.1)	0.89 (0.68- 1.18)
Intra-cervical	10 (4.3)	71 (6.9)	0.69 (0.49- 0.98)**
Circumferential	71 (30.5)	143 (13.7)	2.02 (1.44- 2.84)**
Vesico-uterine	2 (0.9)	19 (1.8)	0.71 (0.27-1.87)
Ureteric	1 (0.4)	19 (1.8)	0.26 (0.05-1.37)
Uretero-vaginal	3 (1.3)	12 (1.2)	1.38 (0.89-2.14)**
Trigonal	11 (4.8)	55 (5.3)	0.74 (0.40-1.37)
Supra-trigonal	5 (2.2)	27 (2.6)	0.69 (0.44-1.06)*
Vault	6 (2.6)	29 (2.8)	0.95 (0.63-1.44)
Small bladder	96 (44.9)	242 (25.0)	2.07 (1.52-2.82)**
Scarring			
No or mild scarring	111 (47.6)	695 (66.9)	Ref
Moderate scarring	82 (35.2)	289 (27.8)	1.55 (1.05-2.29)**
Severe scarring	40 (17.2)	55 (5.3)	2.84 (1.86-4.35)**
>1 fistula	23 (9.9)	52 (5.0)	1.68 (1.11-2.52)**
Cervix not visible	56 (24.1)	157 (15.3)	1.49 (1.00-2.22)*

*p-value<.20
**p-value<.05

Table 4.5: Context of repair and peri-operative procedures by repair outcome

	Not closed N (%)	Closed N (%)	Unadjusted RR (95% CI)
Total (n=1274)	233	1041	
Surgeon experience			
> 200 complex repairs conducted	61 (27.2)	350 (35.5)	1.27 (1.02-1.58)**
Organization of services			
Site			
A (n=71)	19 (8.2)	52 (5.0)	10.86 (4.21-28.02)**
B and C (n=53)	15 (6.4)	38 (3.7)	11.49 (4.37-30.18)**
D (n=246)	61 (26.2)	185 (17.8)	10.07 (4.12-24.58)**
E, G, and I (n=266)	72 (30.9)	194 (18.6)	10.99 (4.52-26.70)**
F and H (n=276)	41 (17.6)	235 (22.6)	6.03 (2.43-14.99)**
J (n=159)	20 (8.6)	139 (13.4)	5.11 (1.96-13.31)**
K (n=203)	5 (2.1)	198 (19.0)	Ref
Repair conducted in the context of training	120 (51.7)	601 (57.8)	0.84 (0.64-1.11)*
Repair conducted in context of outreach services / camp	89 (38.2)	388 (37.4)	0.77 (0.44-1.33)
Intra-operative procedures			
Vaginal-only route of repair	227 (97.4)	989 (95.1)	1.42 (1.11-1.81)**
Single layer suture of bladder	121 (53.1)	677 (67.4)	0.78 (0.57-1.07)*
Double layer suture of bladder	99 (44.0)	314 (31.3)	1.16 (0.84-1.60)
Martius flap (with or without labia skin)	12 (5.3)	31 (3.1)	1.45 (1.10-1.91)**
Relaxing incision	6 (2.7)	10 (1.0)	2.09 (1.35-3.25)**
Post-operative procedures			
Duration of catheterization > 14 days	188 (81.7)	690 (66.9)	2.01 (1.11-3.63)**
Open vs closed drainage system	123 (53.2)	768 (74.1)	0.63 (0.51-0.79)**
Drinking regimen prescribed post-operatively	189 (81.5)	941 (90.6)	0.96 (0.31-2.98)
Prophylactic antibiotics provided post-operatively	202 (87.1)	891 (85.7)	1.04 (0.75-1.43)

*p-value<.20

**p-value<.05

Table 4.6: Association between vaginal route of repair and failure to close the fistula at three month follow-up visit

	Total repaired abdominally / both abdominally and vaginally included in analysis	Total repaired vaginally included in analysis	RR (95% CI)
Unmatched, unadjusted	57	1216	1.42 (1.11-1.81)**
Unmatched, adjusted for indication for abdominal repair			1.72 (1.29-2.29)**
Unmatched, adjusted for indication for abdominal repair, surgeon experience conducting complex repairs, mid-vaginal location			1.40 (1.05-1.87)**
Matched sample, reduced propensity score model	46	92	1.98 (1.27-3.07)**
Matched sample, expanded propensity score model	30	60	1.40 (0.77-2.56)

Table 4.7: The influence of vaginal-only route of repair on repair outcome across levels of indication for abdominal repair in the unmatched sample

	Abdominal approach not indicated		Abdominal approach indicated	
	Closed N (%)	Not closed N (%)	Closed N (%)	Not closed N (%)
Vaginal-only route of repair	637 (99.22)	117 (100.00)	339 (88.05)	108 (94.74)
Abdominal / combined abdominal vaginal	5 (0.78)	0 (00.00)	46 (11.95)	6 (5.26)
RR (95%CI)	--		1.97 (1.03-3.79) **	

Table 4.8: Association between duration of catheterization greater than 14 days and failure to close the fistula at three month follow-up visit

	Total catheterized ≤ 14 days included in analysis	Total catheterized > 14 days included in analysis	RR (95% CI)
Unmatched, unadjusted	383	878	2.04 (1.16-3.59)**
Unmatched, adjusted for prognostic score			1.65 (1.15-2.35)**
Unmatched, adjusted for prognostic score, surgeon experience conducting complex repairs, ureteric involvement			1.62 (1.16-2.26)**
Matched sample, reduced propensity score model	264	542	1.51 (0.93-2.45)
Matched sample, expanded propensity score model	143	297	1.47 (1.04-2.08) **

Table 4.9: The influence of duration of catheterization on repair outcome across levels of severity in the unmatched sample

	Prognostic score <1	Prognostic score ≥ 1
Catheterization for > 14 days vs ≤ 14 days	1.28 (0.77-2.11)	1.95 (1.19- 3.19) **

*p-value<.20
**p-value<.05

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Chapter 5 : Conclusion

Introduction

Vaginal fistula is a devastating, yet preventable condition. The ultimate goal of public health intervention efforts should be to prevent vaginal fistulas from occurring in the first place: specifically, by improving access to emergency obstetric care and the quality of obstetric services in developing countries. However, in the absence of universal access to emergency obstetric care, an immediate goal is to facilitate and improve treatment for women who suffer from the injury. There is currently little evidence regarding patient and fistula characteristics that influence the prognosis of a fistula repair surgery, as well as the comparative effectiveness of various peri-operative procedures on fistula repair outcomes. While clinicians, program implementers and donors alike have called for the development of a standardized system for classifying fistula,[1-5] the development of such a system cannot advance without evidence demonstrating which fistula characteristics are prognostic of repair outcomes and studies which compare the discriminatory value of existing systems. In this dissertation, I sought to fill the above research gaps: first, by reviewing published literature regarding the individual and fistula characteristics, and peri-operative factors that influence repair outcomes; secondly, by comparing existing classification systems with regard to their ability to predict fistula closure, and identifying prognostic factors heretofore not included in existing systems; and finally, by exploring the influence of two repair procedures, one intra-operative and the other post-operative, on fistula closure, independent of measured prognostic factors and indication for repair.

Summary of findings

In Chapter 2, I reviewed the existing literature examining the influence of individual and fistula characteristics, and peri-operative procedures, on fistula repair outcomes. I identified 19 articles meeting the inclusion criteria, all but three of which were observational studies. The surgical outcomes examined were fistula closure, residual incontinence following closure, and closure with no remaining incontinence. No studies demonstrated an influence of patient characteristics on surgical outcomes. With regard to fistula characteristics, the presence of scarring and urethral involvement was associated with poor prognosis across the range of outcomes, with some evidence suggesting an association between greater fistula size and smaller bladder size on poor repair prognosis. Evidence with regard to the role of ureteric involvement and prior repair was insufficient. Most studies examining peri-operative interventions were small, and likely were underpowered to detect small differences. Among the larger studies, results from two RCTs examining prophylactic use of antibiotics and repair outcomes were inconclusive, and a large study examining the influence of use of the Martius graft may have been subject to confounding by indication and provider experience. Studies examining the influence of route of repair and duration of catheterization were likely underpowered and subject to bias resulting from confounding by indication. I thus concluded that while scarring and urethral involvement appear to be associated with poor repair prognosis, overall there remains insufficient evidence on which to base practice.

In Chapter 3, I aimed to advance existing research on the individual patient and fistula characteristics that predict fistula closure, as well as to contribute to efforts in developing a standardized, evidence-based fistula classification system. Specifically, I evaluated the discriminatory value of five existing classification systems in terms of predicting fistula closure, and proposed an empirically-derived prognostic score, informed by these systems. The scoring systems representing the Tafesse, Goh and WHO classification systems had higher predictive values: AUC 0.60 (95%CI: 0.55-0.65), AUC .62 (95%CI: 0.57-0.68) and AUC 0.63 (95%CI: 0.57-0.68), respectively, compared to the Waaldijk system; it was not possible to develop a score for the Lawson system. However, there was no statistically significant difference in the AUCs of these scores. The empirically-derived prognostic score achieved a similar discriminative ability (AUC .62, 95%CI: .56-.67) to the scores representing Tafesse's, Goh's and WHO's systems. Importantly, the existing classification systems evaluated contained overlapping or redundant components, or components that did not independently predict repair outcomes. In contrast, the empirically-derived score contained a minimally sufficient set of non-overlapping and more objectively measured components, and therefore may be simpler to use and have higher reliability. Based on these findings, I concluded that while further evaluation of the reliability and validity of these systems is warranted, consideration should be given to a prognostic score derived empirically from factors shown to independently predict repair outcomes.

In Chapter 4, I endeavored to enrich the evidence-base regarding the comparative effectiveness of peri-operative procedures with regard to surgical repair outcomes by examining two procedures in particular: vaginal versus abdominal route of repair, and urinary catheterization greater than 14 days compared to 14 days or less. Having met published indications for an abdominal route of repair (e.g. intracervical or supratrigonal location) was indeed independently associated with choice of abdominal surgical route (ARR 13.33, 95%CI: 4.61-38.56); few women undergoing abdominal repair did not meet the typical indications. Each unit increase in prognostic score was associated with 1.07 times higher likelihood of urinary catheterization >14 days (95%CI: 1.00-1.13), after adjusting for facility, provider experience, other fistula characteristics and route of repair. Vaginal route of repair was independently associated with increased risk of failure of fistula closure, relative to the abdominal route of repair; however, stratified analyses suggested a particularly elevated risk associated with vaginal route of repair for women in whom an abdominal repair was indicated (RR 1.97, 95%CI: 1.03-3.79). Effect estimation among women in whom a vaginal approach was not indicated was precluded because there were no failed closures among women who underwent abdominal repair despite not meeting indications for abdominal route. Despite adjusting for repair prognosis and provider experience, duration of catheterization >14 days predicted failure to close the fistula (ARR 1.62, 95%CI: 1.16-2.26). Results for both the influence of route of repair and duration of catheterization on fistula closure were similar when analyses were conducted in a propensity score-matched sample.

Implications of the findings

The results presented in this dissertation have important implications for clinical practice. First, I have illustrated that a classification system based solely on fistula location, such as Lawson's system, is unlikely to be informative in terms of repair prognosis. Second, I have demonstrated that the Tafesse, Goh and WHO classification systems can be simplified for the purpose of predicting fistula closure: redundant measures can be streamlined, and non-predictive components could be eliminated from these systems. Third, I have proposed an empirically-derived prognostic score which can be used in the clinical setting, as a complement to clinical judgment for making to triage decisions. This score is simple, comprising a minimal number of non-overlapping components, and is easy to calculate. A threshold value for "poor prognosis" of $\geq$1 (favoring increased sensitivity over specificity) presented in Chapter 4, is easy to recall. In a context where the availability of surgeons with specialized skills is limited, facilitating triage decisions is critical.

It is important to note, however, that the empirically-derived prognostic score presented in this dissertation may have some limitations. For instance, it may not be useful in terms of planning the execution of a repair (e.g. determining which procedures should be undertaken). This was clearly illustrated in Chapter 4: indications for abdominal route of repair, all indicators of visualization of and access to the fistula through a vaginal approach, were the most important predictors of route of repair, while increased prognostic score appeared to be inversely associated with an abdominal route of repair. In addition, and as will be discussed under "Future Directions" below, this score would not be useful for counseling a patient with regard to her likelihood of return to a more functional state, since residual incontinence may be possible despite successful fistula closure. Perhaps most importantly, this score represents only a proxy measure for the difficulty of a fistula repair. While repair prognosis and difficulty of executing a repair are overlapping constructs, difficulty of repair may not necessarily lead to a poor outcome.

The results of this dissertation also have important implications for future research efforts. The above-mentioned prognostic score can be used to facilitate the evaluation of surgical success rates and provider performance across facilities, an issue of particular relevance for program implementers, including local and national health ministries. Such a score can also be used to evaluate the effects of interventions on surgical outcomes independent of confounding by prognosis, as demonstrated in Chapter 4. If widely adopted, such a score could facilitate the comparative analysis of studies that examine treatment outcomes by ensuring that a standard set of components are adjusted for across studies.

Unfortunately, drawing definitive conclusions from the analyses examining the comparative effectiveness of abdominal route of repair and catheterization greater than 14 days (presented in Chapter 4) may not be possible. While it appeared as though the risk of failure to close the fistula for women repaired vaginally was elevated in women in whom access through the vagina was impaired, there were few women in this sample who underwent abdominal repair when it was not indicated. Similarly, residual confounding by indication and reverse causation cannot be excluded as explanations for the increased risk of failure to close the fistula among women catheterized for longer than 14 days. Nonetheless, these analyses highlighted factors that may influence the use of one procedure over another, and confirmed that prognosis of repair and duration of catheterization are indeed related.

Finally, the methods used in this dissertation can serve as a model to future investigations evaluating the discriminatory value of different classification systems, or studies using a multi-site observational study design to compare the effectiveness of peri-operative procedures. This study represents the largest collection of data assessing predictors of fistula repair outcomes to-date, and is the only study designed to follow women after discharge from the facility in order to determine longer-term repair outcomes. The study's large sample size enabled the use of a split-sample design to validate the prognostic models on a dataset independent of the one used to create the models, thereby deriving less biased measures of classification system performance;[6] future studies evaluating different classification systems should consider this design, or should validate their models in different populations. The large sample size also enabled evaluation of the role of route of repair on fistula closure. As demonstrated in Chapter 2, few studies examining predictors of fistula repair outcomes have been sufficiently powered to demonstrate small significant effects. Finally, propensity score analysis may be a useful tool where information on potential prognostic factors is comprehensively collected, or where overlap of covariates across comparison groups is questioned. Notably, where there is little overlap in covariates (and therefore fewer possible matches on propensity score across comparison groups) and many observations have been discarded, researchers should be cautious about the external validity of their results.

Future directions

There are several specific future directions that I would like to highlight. First, Chapter 2 demonstrated the range of outcomes studied (fistula closure, residual incontinence, and any incontinence), and that this, in concert with the range of predictors studied, has resulted in a lack of a unified evidence-base on most predictor-outcome relationships. It is undoubtedly true that from the patient's standpoint, "any incontinence," whether it be due to failure to close the fistula or residual incontinence, is the most important endpoint. However, this endpoint does little to inform intervention efforts, since the distinct roles different patient or fistula characteristics or peri-operative procedures have on fistula closure versus residual incontinence are muddled. Thus, I recommend that when possible, future studies examine fistula closure and residual incontinence separately, in order to clarify the etiological importance of different characteristics and procedures on distinct outcomes. Similarly, I evaluated the discriminatory value of several classification systems on fistula closure, the immediate goal of a fistula repair. However, it is also important to evaluate the discriminatory value of these systems on residual incontinence. A classification system which is prognostic of residual incontinence could have important value for patient counseling, insofar that patients could be given an idea of what their chances of functional success are following the surgery.

In addition to testing the discriminatory value of different classification systems with regard to residual incontinence, there are a number of additional steps that need to take place to further the development of a standardized classification system. First, the utility of a classification system depends not only on its discriminatory ability, but also its ease of use and reliability in a clinical setting. To date, only the Goh classification system has been subjected to tests of inter- and intra-rater reliability. Thus, an important next step would be to test the inter- and intra-rater reliability of the classification systems evaluated in Chapter 3. Most importantly, the acceptance of a particular standardized classification system requires input and buy-in from the gynecologists, urogynecologists and urologists who are performing fistula surgeries. These analyses thus represent only an initial step towards the development of a standardized, evidence-based fistula classification system.

Finally, further research is required to evaluate the effectiveness of different peri-operative procedures used for fistula repair. Reducing the duration of post-operative bladder catheterization by only four days has been shown to have the potential of increasing the number of patients who could receive surgical care by 20% in a high-volume facility,[7] and may be associated with a decreased incidence of UTIs.[8] While further research to evaluate the non-inferiority of shorter duration catheterization is critically needed, in Chapter 4 I demonstrated the limitations of an observational study design in answering this question. Future observational studies on this issue must carefully establish temporality of the relationship between catheterization duration and repair outcome, by recording multiple outcome measurements (dye tests as well as any other methods to assess outcome, such as visual inspection of leaking around the catheter), and their timing relative to catheter removal. Nevertheless, confounding by prognosis of repair may be difficult to avoid in an observational study, particularly since some clinical decisions may be based on factors that are difficult to measure. The relationship between duration of catheterization and repair outcomes would thus be optimally measured within the context of a clinical trial, where the process of randomization would ensure that the control and intervention groups in the study are, on average, similar with respect to all prognostic factors that might confound the association between the intervention and the outcome. The cost and health implications (particularly health-care associated infection) related to longer duration catheterization, together with the lack of evidence with regard to the optimal length of catheterization following pelvic surgery, recent evidence from a canine model indicating that early bladder filling may facilitate bladder healing,[9] and the range of catheter durations currently prescribed in practice, lend justification to the conduct of such a trial.

Further research is similarly necessary to determine the optimal route of repair for urinary fistula. However, an RCT may not be warranted to evaluate the effectiveness of abdominal route of repair. Abdominal approach of repair is primarily performed under general anesthesia, which requires additional clinical skills, is more expensive than local anesthetia,[10] and may not be routinely available in low-resource settings. Moreover, abdominal repairs have been found to be associated with increased blood loss,[10, 11] UTI[10] and longer hospital stay compared to vaginal repairs.[11] Thus, given the decreased likelihood that an RCT would lead to an intervention that can be practically implemented, the effectiveness of this intervention would be better studied in the context of an observational cohort study. Such a study would need to be adequately powered to test hypotheses of effect measure modification; specifically, whether abdominal route of repair is warranted for certain patient populations (defined by fistula characteristics) compared to others, or whether the effectiveness of an abdominal route of repair varies by provider experience or training. An opportunity for such large-scale observational research exists in the form of the Geneva Foundation for Medical Education and Research (GFMER) web-based data entry system,[12] which aims to enable the collection and evaluation of prospective data related to patient characteristics and peri-operative procedures used, among other objectives. Because this database can be administered and managed from multiple centers, its wide-scale adoption would allow for the large-scale collection of data that is needed to examine relatively rare procedures.

Conclusion

This dissertation has contributed to the body of evidence on obstetric fistula care and treatment in the following ways: 1) through summarizing what is known with regard to a range of predictors of fistula repair outcomes; 2) by comparing the discriminatory value of existing classification systems in predicting fistula closure; 3) by identifying a minimally sufficient set of patient and fistula characteristics prognostic of fistula closure; 4) by elucidating factors that influence abdominal route of repair and duration of catheterization longer than 14 days; and finally, 5) through examining the comparative effectiveness of the latter procedures on repair outcomes, and whether outcomes vary by indication for repair and repair prognosis. The care and treatment of fistula patients in developing countries is fraught with many challenges; continuing research on this important topic can help to ensure that a lack of an evidence-base is not among them.

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Methodological appendices

Appendix A: Diagrams of types of urinary fistula [i]

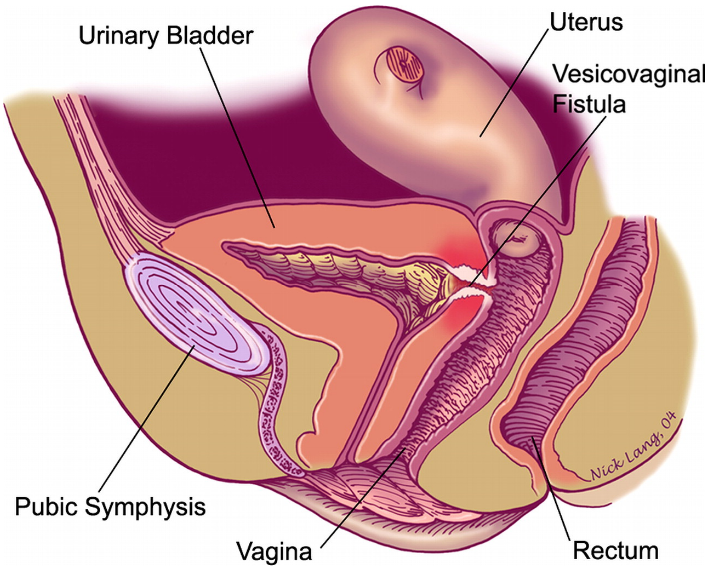


Figure A.1: Lateral view of a vesicovaginal fistula
Reprinted with permission from R. Avritscher and the Radiological Society of North America (RSNA)

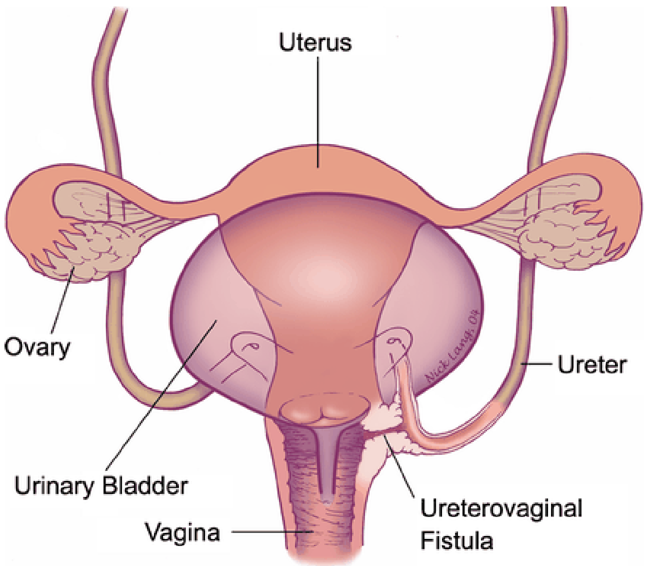


Figure A.2: Left ureterovaginal fistula
Reprinted with permission from R. Avritscher and the Radiological Society of North America (RSNA)

[i] Avritscher R, Madoff DC, Ramirez PT, Wallace MJ, Ahrar K, Morello FA, et al. Fistulas of the Lower Urinary Tract: Percutaneous Approaches for the Management of a Difficult Clinical Entity. Radiographics. 2004 October 1, 2004;24(suppl 1):S217-S36.

Appendix B: Glossary

Table B.1: Glossary of key terms and phrases

Term	**Definition**
Any incontinence	Failure to close the fistula or residual incontinence
Circumferential fistula	Complete separation of the urethra and bladder
Closing mechanism	Variously defined as the urethral sphincter, or continence mechanism
Closure (of the fistula)	State in which fistula has been surgically rendered intact, with no leakage of urine around the sutures.
Continence mechanism	The combination of anatomical structures that contribute to continence, including a functioning urethral sphincter, quiescent bladder, and functioning musculofascial supports.
Intra-cervical fistula	Fistula between the bladder and the cervical canal
Juxta-cervical fistula	Fistula located in the region of the cervix
Juxta-urethral fistula	Fistula at the urethro-vesical junction
Mid-vaginal fistula	Small defect 4 cm or more from the external urethral orifice
Obstetric fistula	Vaginal fistula of obstetric etiology
Recto-vaginal fistula (RVF)	Fistulas located between the rectum and the vagina
Residual incontinence	Remaining incontinence (stress incontinence, urge incontinence, frequency / urgency syndrome) following successful fistula closure
Urinary fistula	Term used to refer to a vaginal fistula which results in urinary incontinence
Vault fistula	Fistulas located at the vaginal apex
Vesico-vaginal fistula (VVF)	Fistulas located between the bladder and the vagina
Vaginal fistula	Abnormal passageway between the vagina and bladder or between the vagina and rectum

Appendix C: Existing classification systems compared in Chapter 1

Where possible, we retained the original components of the classification schemes that we tested. However, in some cases, it was necessary to approximate the measures, either because we did not measure the component exactly, or for analytic purposes. The original measures and ways in which they were operationalized are shown below.

Table C.1: Lawson, Waaldijk, Tafesse and Goh classification systems and how they were operationalized for analytic purposes

Classification system	**Type and / or description of fistula**	**How component was operationalized**
Lawson 1968	i. Juxta-urethral ii. Mid-vaginal iii. Juxta-cervical iv. Vault v. Massive combination fistula	i. No change ii. No change iii. No change iv. No change v. No change
Waaldijk 1995	<u>Classification</u> Type 1 Not involving the closing mechanism Type 2 Involves closing mechanism A *Without* (sub)total urethra involvement B *With* (sub)total urethra involvement a *Without* circumferential defect b *With* circumferential defect Type 3 Ureteric and other exceptional fistulas	<u>Classification</u> Type 1 Not involving the closing mechanism and not involving complete destruction of bladder neck Type 2 Involves closing mechanism or destruction of bladder neck A Intact or partially damaged urethra (no change) B Completely destroyed urethra (no change) a No change b No change Type 3 Mixed vesicovaginal and rectovaginal fistulas, cervical and ureteric fistulas
	<u>Size</u> Small <2 Medium 2-3 Large 4-5 Extensive≥ 6	<u>Size</u> No change No change No change No change

Classification system	Type and / or description of fistula	How component was operationalized
Tafesse 2008	Class 1 Non-circumferential, not previously operated Class 2 Non-circumferential, previously operated Class 3 Circumferential, not previously operated Class 4 Circumferential, previously operated	Class 1 No change Class 2 No change Class 3 No change Class 4 No change
	Urethral involvement I No involvement (urethral length>4cm) II Urethra involved but not middle 1/3 (urethral length 2.7-3.9 cm) III Middle 1/3 partly involved (urethral length 1.4-2.6 cm) IV Middle 1/3 completely involved but some urethral tissue remains (urethral length <1.4 cm) V No urethra	Urethral involvement I No change II No change III No change IV Collapsed categories IV and V
	Bladder size a Longitudinal diameter >7 cm b Longitudinal diameter 4-7 cm c Longitudinal diameter <4 cm	Bladder size a "Normal" bladder b Small bladder c Small bladder
	Anterior vaginal tissue loss 1 Less than 50% of anterior vagina is involved (>3.5 cm of healthy vagina remains) 2 More than 50% of the anterior vagina wall is involved (<3.5 cm of health vagina remains) 3 Obliterated vagina (vagina cannot admit more than 1 finger)	Anterior vaginal tissue loss 1 Minimal tissue loss 2 Moderate tissue loss 3 Extensive tissue loss or obliterated vagina

Classification system	Type and / or description of fistula	How component was operationalized
Goh 2004	Type 1 Distal edge of the fistula >3.5 cm from external urinary meatus Type 2 Distal edge of the fistula 2.5-3.5 cm from external urinary meatus Type 3 Distal edge of the fistula 1.5-<2.5 cm from external urinary meatus Type 4 Distal edge of the fistula <1.5 cm from external urinary meatus	Type 1 Urethral length > 3.5 cm Type 2 Urethral length 2.5-3.5 cm Type 3 Urethral length 1.5-<2.5 cm Type 4 Urethral length <1.5 cm
	a Size <1.5 cm in the largest diameter b Size 1.5-3 cm in the largest diameter c Size >3 cm in the largest diameter	a No change b No change c No change
	i. None or only mild fibrosis (around fistula and/or vagina) and/or vaginal length >6cm, normal bladder capacity ii. Moderate or severe fibrosis (around fistula and/or vagina) and/or reduced vaginal length and/or bladder capacity iii. Special considerations, e.g. post-radiation, ureteric involvement, circumferential fistula, previous repair	i. None or only mild fibrosis and normal bladder capacity ii. Moderate or severe fibrosis and small bladder capacity iii. Ureteric involvement, circumferential fistula, previous repair

Table C.2: Classification system presented by WHO and how it was operationalized for analytic purposes

Classification system	Type and / or description of fistula			How component was operationalized
WHO	Defining Criteria	Simple	Complex	
	Number of fistula	▪ single	▪ multiple	▪ No change
	Site	▪ vesico-vaginal (VVF)	▪ All non-VVF urinary fistula ▪ recto-vaginal (RVF) ▪ mixed VVF/RVF ▪ involvement of cervix	▪ non-VVF excludes ureteric and urethral fistulas
	Size (diameter)	▪ <4cm	▪ >4cm	▪ No change
	Involvement of the urethra / continence mechanism	▪ absent	▪ present	▪ No change
	Scarring of vaginal tissue	▪ absent	▪ present	▪ No change
	Presence of circumferential defect*	▪ absent	▪ present	▪ Not included in multivariate analysis
	Degree of tissue loss	▪ minimal	▪ extensive	▪ Moderate and minimal tissue loss considered "minimal"
	Ureter/bladder involvement	▪ ureters are inside the bladder, not draining into the vagina	▪ one or both ureters are draining into the vagina ▪ one or both ureters are at the edge of the fistula	▪ Created composite measure representing ureteric involvement (either ureteric location or ureters draining into vagina or at edge of vagina)
	Number of previous repair attempts	▪ no previous attempt	▪ failed previous repair attempts	▪ No change

***** Complete separation of the urethra and bladder

Appendix D: Comparing discriminatory value of classification systems, accounting for clustering by surgeon rather than site

In this appendix, I evaluate the discriminatory value of existing classification systems and propose an empirically-derived prognostic score, accounting for provider, rather than site, as the clustering variable in my analyses. The predictive value of existing systems remained the same. One variable, partial urethral involvement, in the empirically-derived prognostic score was no longer significant. There were no statistically significant differences in the AUCs in the proposed empirically-derived prognostic score, and the scores developed to represent the Tafesse, Goh and WHO classification systems. I present results of analyses accounting for clustering by site rather than provider within the body of the manuscript, since site is the higher order level of clustering.

Table D.1: Existing classification systems – clustering by provider rather than site

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
Lawson						
	Juxta-urethral	24 (20.5)	105 (20.4)	1.14 (0.80-1.62)	0.93 (0.60-1.43)	-
	Mid-vaginal	20 (17.1)	172 (33.2)	0.58 (0.36-0.92)**	0.52 (0.32-0.86)**	-2
	Juxta-cervical	20 (17.1)	87 (16.9)	0.93 (0.57-1.52)	0.81 (0.52-1.27)	-
	Vault	2 (1.7)	17 (3.3)	0.62 (0.24-1.63)	0.52 (0.19-1.46)	-
	Massive combination	2 (1.7)	5 (1.0)	1.67 (0.74-3.79)	-	-
Waaldijk						
	Type 1 Not involving closing mechanism	101 (84.9)	490 (94.8)	Ref	Ref	-
	Type 2 Involves closing mechanism	18 (15.3)	27 (5.2)	2.32 (1.71-3.16)**	Ref	-
	Type 2Aa Without (sub)total urethra involvement without circumferential defect	8 (6.8)	9 (1.7)	2.49 (1.59-3.90)**	2.70 (1.70-4.08)**	3
	Type 2Ab Without (sub)total urethra involvement with circumferential defect	6 (5.1)	13 (2.5)	1.81 (0.87-3.73)*	1.67 (0.83-3.37)*	-
	Type2Ba With (sub)total urethra involvement without circumferential defect	1 (0.9)	3 (0.6)	1.34 (0.44-4.07)	1.69 (0.70-4.08)	-
	Type2Bb With (sub)total urethra involvement with circumferential defect	2 (1.7)	1 (0.2)	3.63 (2.30-5.73)	3.50 (1.26-5.42)**	4

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
	Type 3 Ureteric and other exceptional fistulas[ii]	39 (33.1)	128 (24.7)	1.39 (0.85-2.30)*	1.31 (0.82-2.12)*	-
	Small <2	27 (23.7)	143 (29.1)	Ref	Ref	-
	Medium 2-3	49 (42.6)	254 (51.7)	0.91 (0.61-1.34)	0.95 (0.65-1.38)	-
	Large 4-5	31 (27.0)	75 (15.3)	1.62 (1.03-2.56)	1.38 (0.97-1.97)*	-
	Extensive≥ 6	7 (6.1)	22 (4.5)	1.31 (0.66-2.58)	1.17 (0.61-2.23)	-
Tafesse						
	Class 1 Non-circumferential, not previously operated	50 (42.4)	352 (67.8)	Ref	Ref	-
	Class 2 Non-circumferential, previously operated	28 (23.7)	98 (18.9)	1.78 (0.97-3.25**	1.73 (0.93- 3.23)*	-
	Class 3 Circumferential, not previously operated	29 (24.6)	57 (11.0)	2.63 (1.43-4.84)**	1.95 (1.05-3.62)**	2
	Class 4 Circumferential, previously operated	11 (9.3)	12 (2.3)	3.37 (1.94-5.84)**	2.28 (1.27-4.11)**	2
	I No urethral involvement (urethral length>4cm)	12 (11.9)	116 (25.4)	Ref	Ref	-
	II Urethra involved but not middle 1/3 (2.7-3.9 cm)	47 (46.5)	182 (39.9)	2.27 (103- 5.01)**	1.86 (1.27-3.74)**	2
	III Middle 1/3 partly involved (1.4-2.6 cm)	34 (33.7)	142 (31.1)	2.23 (1.05- 4.74)**	1.35 (0.67-2.72)	-
	IV-V Middle 1/3 completely involved or no urethra[iii]	8 (7.9)	16 (3.5)	3.85 (1.59- 9.35)**	2.17 (1.10- 4.29)*	2
	b-c Longitudinal diameter of bladder ≤ 7 cm[iv]	44 (40.7)	119 (24.4)	2.03 (1.19-3.43)**	1.19 (0.78-1.80)	-
	< 50% of anterior vagina involved	34 (28.8)	292 (56.5)	Ref	Ref	-
	> 50% of the anterior vagina wall involved	53 (44.9)	190 (36.8)	1.65 (1.02- 2.67)**	1.57 (1.21-2.04)**	2
	Obliterated vagina	31 (26.3)	36 (7.0)	3.36 (1.97-5.73)**	2.64 (2.17- 3.21)	3
Goh						
	Type 1 Distal edge of the fistula >3.5 cm from external urinary meatus (EUM)	20 (18.3)	165 (32.9)	Ref	Ref	-
	Type 2 Distal edge of the fistula 2.5-3.5 cm from EUM	47 (46.5)	180 (39.5)	2.50 (1.16- 5.30)	1.98 (1.280-3.05)**	2

[ii] This category includes mixed vesicovaginal and rectovaginal fistula, cervical and ureteric fistula. Urethral fistula are excluded from this category since these are measured by other components, and uniquely rectovaginal fistula are excluded since our analyses examine closure of urinary fistula

[iii] Categories IV (Middle 1/3 completely involved but some urethral tissue remains (urethral length <1.4 cm)) and V (no urethra) were collapsed due to the presence of only 1 woman in the latter category

[iv] Categories b (Longitudinal diameter 4-7 cm) and c (Longitudinal diameter <4 cm) collapsed and equated with “small” or “no bladder” in our dataset

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
	Type 3 Distal edge of the fistula 1.5-<2.5 cm from EUM	27 (26.7)	120 (26.3)	2.28 (1.07- 4.87)	1.62 (1.01-2.59)**	2
	Type 4 Distal edge of the fistula <1.5 cm from EUM	15 (14.9)	37 (8.1)	3.74 (1.75- 7.99)	2.04 (1.17-3.57)**	2
	a Size <1.5 cm	21 (18.4)	107 (21.7)	Ref	Ref	-
	b Size 1.5-3 cm	49 (43.0)	273 (55.5)	0.90 (0.53-1.53)	0.75 (0.44-1.26)	-
	c Size >3 cm	44 (38.6)	112 (22.8)	1.69 (1.05-2.70)	0.98 (0.65-1.47)	-
	i. None or only mild fibrosis, and/or vaginal length >6cm, normal bladder capacity	Ref	Ref	Ref	Ref	-
	ii. Moderate or severe fibrosis, and/or reduced vaginal length and/or bladder capacity	75 (63.6)	216 (41.6)	2.07 (1.23- 3.48)	1.74 (1.10-2.77)**	2
	iii. Special considerations, e.g. post-radiation, ureteric involvement, circumferential fistula, previous repair	73 (61.9)	218 (42.0)	1.87 (0.99-3.54)*	1.55 (0.81-2.96)*	-
WHO						
	>1 fistula	16 (13.6)	24 (4.6)	2.26 (1.43-3.56)**	1.83 (1.06-3.16)**	2
	Site (mixed vvf rvf or cervical fistula[v])	8 (6.8)	47 (9.1)	0.72 (0.40-1.30)	0.78 (0.39-1.56)	-
	Size (diameter >4 cm)	38 (33.3)	95 (19.3)	1.72 (1.13-2.62)**	1.17 (0.83- 1.66)	-
	Involvement of the urethra / continence mechanism	72 (61.0)	192 (37.1)	2.03 (1.52-2.70)**	1.64 (1.20-2.24)**	2
	Scarring	94 (79.7)	386 (74.5)	0.86 (0.36-2.09)	0.97 (0.57-1.65)	-
	Circumferential defect	40 (33.9)	69 (13.3)	2.32 (1.60-3.35)**	-	-
	Extensive tissue loss	31 (26.3)	35 (6.8)	2.75 (1.80-4.18)**	1.89 (1.24-2.86)**	2
	Ureter involvement[vi]	32 (27.4)	87 (16.9)	1.67 (1.00-2.80)*	1.13 (0.69-1.86)	-
	Previous repair	39 (33.1)	110 (21.2)	1.57 (1.07-2.31)**	1.43 (0.96-2.13)*	-

[v] In this category are included mixed vesicovaginal and rectovaginal fistula and cervical fistula. Urethral fistula are excluded from this category since these are measured by the component "involvement of the urethra / continence mechanism." Ureteric fistula are excluded as they are measured through the variable "ureter involvement" and uniquely rectovaginal fistula are excluded since our analyses examine closure of urinary fistula

[vi] This variable is a proxy for the WHO variable "ureters draining into the vagina or at edge of the fistula": non-specified ureteric involvement was included here to avoid overlap with the variable "non-vvf"

Table D.2: Additional variables for consideration in a prognostic classification system – accounting for clustering by provider rather than site

Component	Open N (%)	Closed N (%)	RR (95% CI)
Patient characteristics			
Age > 25	65 (55.1)	241 (46.4)	1.19 (0.84-1.70)
Duration of fistula (average years, sd)	5.5 (8.3)	3.0 (4.7)	1.04 (1.03-1.06)**
Comorbidities present at baseline			
Genital cutting	35 (29.7)	99 (19.2)	1.26 (0.90-1.87)
Malnutrition	8 (6.8)	31 (6.0)	1.26 (0.71-2.23)
Anemia	9 (7.6)	36 (6.9)	1.14 (0.75-1.74)
UTI	0 (0.0)	2 (0.4)	-
HIV	0 (0.0)	2 (0.4)	-
Malaria	1 (0.8)	3 (0.6)	0. 59 (0.35-2.58)
Helminthiasis	20 (16.9)	54 (10.4)	1.23 (0.83-1.82)
Fistula characteristics not included in above classification systems			
Necrotic tissue present	16 (13.7)	46 (8.9)	1.44 (0.64-3.23)
No or mild scarring	51 (43.2)	356 (68.7)	Ref
Moderate scarring	43 (36.4)	133 (25.7)	1.85 (1.10-3.13)**
Severe scarring	24 (20.3)	29 (5.6)	3.39 (1.98-5.80)**
No urethral involvement	46 (39.0)	326 (62.9)	Ref
Partial urethral involvement	30 (25.4)	119 (23.0)	1.50 (1.03-2.17)**
Complete destruction or transection / circumferential injury	41 (35.0)	72 (14.0)	2.64 (1.88-3.72)**
Any ureteric involvement	78 (66.7)	266 (51.6)	1.67 (1.00-2.80)*
Non-vvf (ureteric, urethral, rectovaginal, cervical fistula)	27 (22.9)	79 (15.4)	1.65 (1.14-2.38)**
Cervix not visible	65 (55.1)	241 (46.4)	1.37 (0.78-2.44)

Table D.3: Proposed fistula complexity scoring system – outcome at follow-up, adjusting for clustering by provider

Component	ARR (95% CI)	Score
>1 fistula	2.03 (1.21- 3.39)	2
Moderate or severe scarring	1.75 (1.14- 2.70)	2
Complete destruction or transection / circumferential injury	2.04 (1.38- 3.02)	2

Table D.4: Comparison of AUCs – clustering by provider

	Derived cohort		Validation cohort	
Scoring system	**Proportion failed closures**	**C-statistic (95%CI)**	**Proportion failed closures**	**C-statistic (95%CI)**
Waaldijk		0.53 (0.51-0.56)		0.51 (0.49- 0.53)
0	108/616 (17.53%)		110/617 (17.83%)	
3	8/17 (47.06%)		3/12 (25.00%)	
4	2/3 (66.67%)		2/5 (40.00%)	
Goh		0.62 (0.57- 0.67)		0.62 (0.57- 0.68)
0	14/141 (9.93%)		18/141 (12.77%)	
2	44/275 (16.00%)		33/274 (12.04%)	
4	60/221 (27.15%)		64/222 (28.83%)	

	Derived cohort		Validation cohort	
Scoring system	**Proportion failed closures**	**C-statistic (95%CI)**	**Proportion failed closures**	**C-statistic (95%CI)**
Tafesse		0.66 (0.61-0.71)		0.59 (0.54- 0.64)
0	18/193 (9.33%)		18/193 (9.33%)	
2	37/250 (14.80%)		51/230 (22.17%)	
3	63/194 (32.97%)		46/214 (21.50%)	
WHO		0.69 (0.64-0.74)		0.63 (0.57- 0.68)
0	32/337 (9.50%)		44/351 (12.54%)	
2	54/233 (23.18%)		44/215 (20.47%)	
4	32/67 (47.76%)		27/71 (38.03%)	
Proposed		0.69 (0.64-0.74)		0.60 (0.55-0.66)
0	33/355 (9.30%)		48/348 (13.79%)	
2	47/186 (25.27%)		36/194 (18.56%)	
4	3831/96 (39.58%)		31/95 (32.63%)	

Figure D.1: ROC curves – outcome at discharge, derived cohort

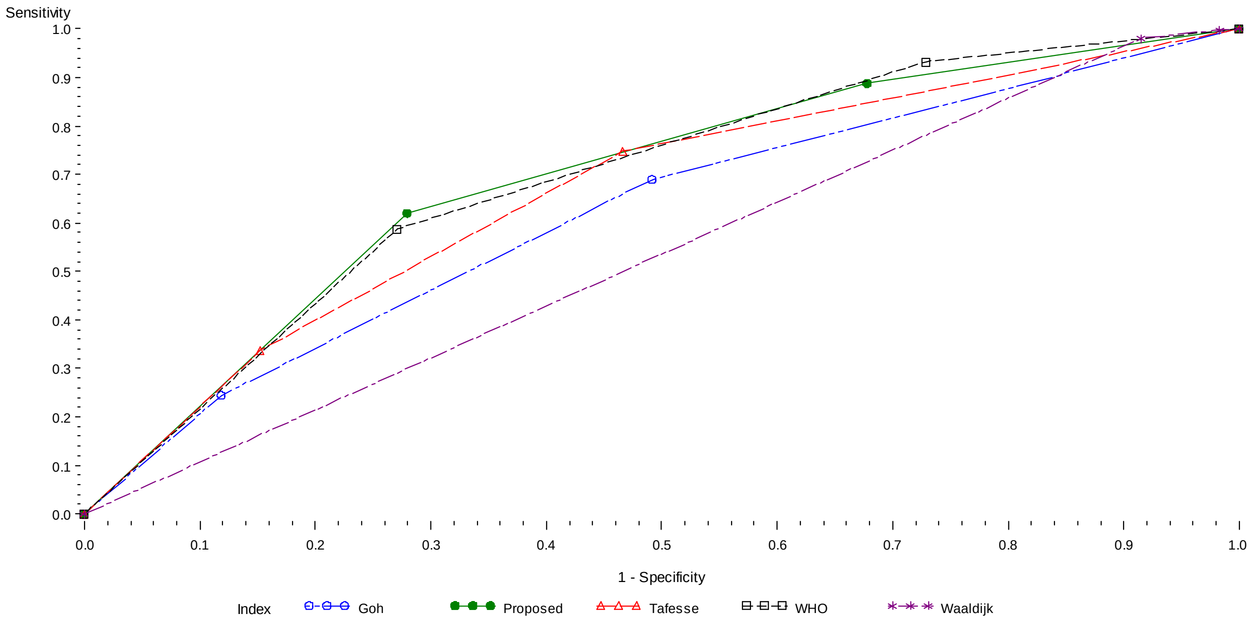
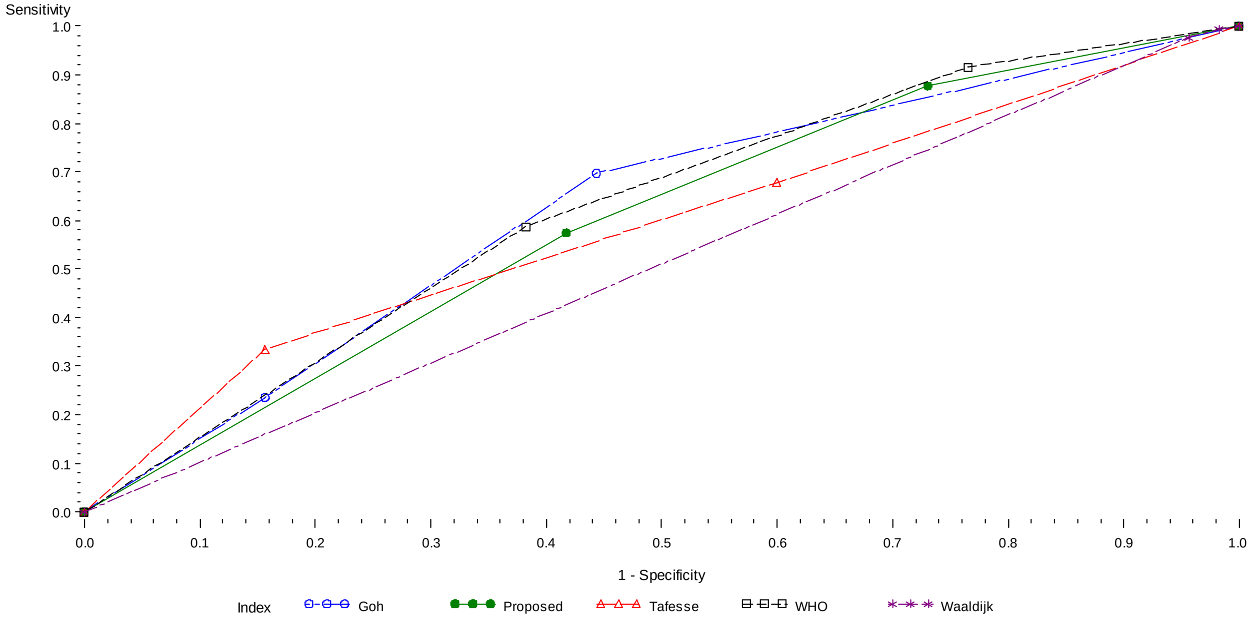


Figure D.2: ROC curves – outcome at discharge, validation cohort



Appendix E: Comparing discriminatory value of classification systems, where primary outcome is fistula closure at discharge from facility

In this appendix, I evaluate the discriminatory value of existing classification systems and propose an empirically-derived prognostic score, examining fistula closure at discharge from the facility, rather than at the three-month follow-up visit. This analysis generated different results than those obtained examining fistula closure at follow-up. Specifically, the components of existing systems that met criteria for inclusion in a scoring system varied (only one element of both the Waaldijk and Goh systems met criteria for inclusion), as did the weights assigned to components previously included. The proposed prognostic score contained one new component (bladder size) and no longer included partial urethral involvement. Further, there was overlap in the confidence intervals across the three AUCs compared. However, prevalence of failure to close the fistula at discharge (15.1%) was lower than at 3-months following surgery (18.5%), and therefore these analyses may have had decreased statistical power for detecting small differences.

Table E.1: Derivation of prognostic scores for existing classification systems –outcome at discharge

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
Lawson						
	Juxta-urethral	22 (22.4)	111 (20.2)	1.18 (0.80-1.75)	0.91 (0.53-1.56)	-
	Mid-vaginal	18 (18.4)	176 (31.8)	0.58 (0.30-1.12)*	0.53 (0.26-1.08)*	-
	Juxta-cervical	14 (14.3)	94 (17.1)	0.81 (0.38-1.72)	0.69 (0.35-1.36)	-
	Vault	2 (2.0)	18 (3.3)	0.68 (0.37-1.26)	0.54 (0.24-1.24)*	-
	Massive combination	2 (2.0)	5 (0.9)	2.25 (1.01-5.03)**	--	-
Waaldijk						
	Type 1 Not involving closing mechanism	85 (85.9)	520 (93.9)	Ref	Ref	-
	Type 2 Involves closing mechanism	14 (14.1)	34 (6.1)	1.97 (1.26-3.09)**	Ref	-
	Type 2Aa *Without* (sub)total urethra involvement without circumferential defect	4 (4.0)	15 (2.7)	1.32 (0.46-3.79)	1.63 (0.62-4.27)	-
	Type 2Ab *Without* (sub)total urethra	6 (6.1)	13 (2.3)	1.92 (0.89-4.18)*	1.54 (0.77-3.08)	-

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
	involvement with circumferential defect					
	Type2Ba *With* (sub)total urethra involvement without circumferential defect	1 (1.0)	3 (0.5)	1.92 (0.82-4.45)*	1.85 (0.71-4.82)	-
	Type2Bb *With* (sub)total urethra involvement with circumferential defect	2 (2.0)	2 (0.4)	3.32 (1.70-6.50)**	2.41 (1.07-5.43)**	2
	Type 3 Ureteric and other exceptional fistula[vii]	37 (37.8)	135 (24.3)	1.73 (1.07-2.80)**	1.53 (0.95-2.49)*	-
	Small <2	20 (21.5)	153 (29.0)	Ref	Ref	-
	Medium 2-3	38 (40.9)	268 (50.8)	1.09 (0.75-1.58)	1.07 (0.73-1.56)	-
	Large 4-5	29 (31.2)	83 (15.7)	2.11 (1.26-3.53)**	1.63 (0.97-2.75) *	-
	Extensive≥ 6	6 (6.5)	24 (4.5)	1.57 (0.73-3.39)	1.33 (0.67-2.62)	-
Tafesse						
	Class 1 Non-circumferential, not previously operated	44 (44.4)	368 (66.3)	Ref	Ref	-
	Class 2 Non-circumferential, previously operated	19 (19.2)	109 (19.6)	1.26 (0.76-2.09)	1.19 (0.64-2.22)	-
	Class 3 Circumferential, not previously operated	28 (28.3)	63 (11.4)	2.65 (1.58-4.44)**	1.74 (0.85-3.58)*	-
	Class 4 Circumferential, previously operated	8 (8.1)	15 (2.7)	2.68 (1.63-4.40)**	1.74 (0.83-3.64)*	-
	I No urethral involvement (urethral length>4cm)	21 (22.8)	169 (31.7)	Ref	Ref	-
	II Urethra involved but not middle 1/3 (2.7-3.9 cm)	29 (34.9)	205 (42.4)	1.42 (0.83-2.41)*	1.18 (0.80-1.73) *	-
	III Middle 1/3 partly involved (1.4-2.6 cm)	34 (41.0)	142 (29.3)	2.23 (1.38-3.61)**	1.37(0.77-2.43)	-
	IV-V Middle 1/3 completely involved or no urethra[viii]	8 (9.6)	17 (3.5)	3.75 (1.98- 7.13)**	2.14 (1.07-4.30) **	2
	b-c Longitudinal diameter of bladder ≤ 7 cm[ix]	37 (43.0)	129 (24.8)	2.17 (1.61-2.93)**	1.13 (0.79-1.63)	-
	< 50% of anterior vagina involved	27 (27.3)	303 (54.9)	Ref	Ref	-
	> 50% of the anterior vagina wall involved	44 (44.4)	209 (37.9)	1.83 (1.20-2.79)**	1.64 (1.08-2.51) **	2
	Obliterated vagina	28 (28.3)	41 (7.4)	3.97 (2.65-5.94)**	3.16 (2. 02-3.95)	3

[vii] This category includes mixed vesicovaginal and rectovaginal fistula, cervical and ureteric fistula. Urethral fistula are excluded from this category since these are measured by other components, and uniquely rectovaginal fistula are excluded since our analyses examine closure of urinary fistula

[viii] Categories IV (Middle 1/3 completely involved but some urethral tissue remains (urethral length <1.4 cm)) and V (no urethra) were collapsed due to the presence of only 1 woman in the latter category

[ix] Categories b (Longitudinal diameter 4-7 cm) and c (Longitudinal diameter <4 cm) collapsed and equated with “small” or “no bladder” in our dataset

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
					**	
Goh						
	Type 1 Distal edge of the fistula >3.5 cm from external urinary meatus (EUM)	21 (22.8)	172 (32.3)	Ref	Ref	-
	Type 2 Distal edge of the fistula 2.5-3.5 cm from EUM	29 (34.9)	203 (41.9)	1.44 (0.87-2.38)	1.14 (0.72-1.80)	-
	Type 3 Distal edge of the fistula 1.5-<2.5 cm from EUM	27 (32.5)	120 (24.8)	2.13 (1.35-3.35)**	1.52 (0.85-2.72)*	-
	Type 4 Distal edge of the fistula <1.5 cm from EUM	15 (18.1)	38 (7.9)	3.38 (1.94-5.89)	1.83 (0.83-4.05)*	-
	a Size <1.5 cm	16 (17.2)	115 (21.8)	Ref	Ref	-
	b Size 1.5-3 cm	36 (38.7)	289 (54.7)	0.95 (0.56-1.59)	0.75 (0.43-1.33)	-
	c Size >3 cm	41 (44.1)	124 (23.5)	195 (1.11-3.44)**	1.02 (0.57-1.83)	-
	i. None or only mild fibrosis, and/or vaginal length >6cm, normal bladder capacity	Ref	Ref	Ref	Ref	-
	ii. Moderate or severe fibrosis, and/or reduced vaginal length and/or bladder capacity	69 (69.7)	231 (41.6)	2.55 (1.82-3.58)**	2.38 (1.54-3.67)**	2
	iii. Special considerations, e.g. post-radiation, ureteric involvement, circumferential fistula, previous repair	59 (59.6)	241 (43.4)	1.66 (0.99-2.80)*	1.25 (0.70-2.21)	-
WHO						
	>1 fistula	14 (14.1)	26 (4.7)	2.33 (1.68- 3.22)**	2.46 (1.60-3.79)**	2
	Site (mixed vvf rvf or cervical fistula[x])	8 (8.1)	48 (8.6)	0.94 (0.66-1.34)	0.91 (0.68-1.21)	-
	Size (diameter >4 cm)	35 (37.6)	107 (20.3)	1.90 (1.24-2.91)**	1.13 (0.80-1.61)	-
	Involvement of the urethra / continence mechanism	59 (59.6)	213 (38.4)	2.01 (1.36-2.97)**	1.61 (0.99-2.62)*	-
	Scarring	83 (83.8)	409 (73.8)	2.16 (1.54-3.04)**	1.84 (1.03-3.27)**	2
	Circumferential defect[xi]	36 (36.4)	78 (14.1)	2.49 (1.76-3.53)**	-	-
	Extensive tissue loss	28 (28.3)	40 (7.2)	2.90 (2.19-3.84)**	2.03 (1.52-2.71)**	2
	Ureter involvement[xii]	29 (29.6)	94 (17.1)	1.82 (1.09-3.06)**	1.25 (0.84-1.86)*	-

[x] In this category are included mixed vesicovaginal and rectovaginal fistula and cervical fistula. Urethral fistula are excluded from this category since these are measured by the component "involvement of the urethra / continence mechanism." Ureteric fistula are excluded as they are measured through the variable "ureter involvement" and uniquely rectovaginal fistula are excluded since our analyses examine closure of urinary fistula

[xi] This variable was not included in multivariate analysis since circumferential fistulas are a type of urethral involvement, captured by another component

[xii] This variable is a proxy for the WHO variable "ureters draining into the vagina or at edge of the fistula": non-specified ureteric involvement was included here to avoid overlap with the variable "non-vvf"

	Component	Open N (%)	Closed N (%)	RR (95% CI)	ARR (95% CI)	Score
	Previous repair	27 (27.3)	124 (22.3)	1.11 (0.76-1.63)	1.01 (0.70-1.47)	-

Table E.2: Additional variables for consideration in a prognostic classification system – outcome at discharge

Component	Open N (%)	Closed N (%)	RR (95% CI)
Patient characteristics			
Age > 25	50 (50.5)	266 (47.9)	0.94 (0.59-1.49)
Duration of fistula (average years, sd)	4.3 (7.1)	3.2 (5.3)	1.03 (1.01-1.05)**
Comorbidities present at baseline			
Genital cutting	22 (22.2)	113 (20.5)	1.05 (0.61-1.81)
Malnutrition	13 (13.1)	32 (5.8)	1.68 (1.17-2.41)**
Anemia	12 (12.1)	38 (6.8)	1.16 (0.45-3.00)
UTI	0 (0.0)	2 (0.4)	-
HIV	0 (0.0)	2 (0.4)	-
Malaria	1 (1.0)	3 (0.6)	1.59 (0.89-2.83)
Helminthiasis	12 (12.1)	62 (11.2)	1.03 (0.95-1.12)
Fistula characteristics not included in above classification systems			
Necrotic tissue present	15 (15.3)	52 (9.5)	1.40 (0.57-3.46)
No or mild scarring	37 (37.4)	379 (68.4)	Ref
Moderate scarring	40 (40.4)	142 (25.6)	2.33 (1.62-3.37)**
Severe scarring	22 (22.2)	33 (6.0)	4.20 (2.68-6.56)**
No urethral involvement	40 (40.4)	342 (61.7)	Ref
Partial urethral involvement	22 (22.2)	129 (23.3)	1.42 (1.03-1.95)**
Complete destruction or transection / circumferential injury	37 (37.4)	81 (14.8)	2.75 (1.84-4.11)**
Any ureteric involvement	29 (29.6)	94 (17.1)	1.82 (1.09-3.06)**
Non-vvf (ureteric, urethral, rectovaginal, cervical fistula)	68 (68.7)	285 (51.7)	1.94 (1.28-2.96)**
Cervix not visible	23 (23.2)	86 (15.7)	1.64 (1.14-2.33)**

Table E.3: Proposed prognostic score – outcome at discharge

Component	ARR (95% CI)	Score
Small bladder	1.21 (1.01- 1.45)	1
>1 fistula	2.11 (1.41- 3.17)	2
Moderate or severe scarring	2.02 (1.57- 2.60)	2
Complete destruction or transection / circumferential injury	2.07 (1.52- 2.83)	2

Table E.4: Performance of selected classification systems – outcome at discharge

	Derived cohort		Validation cohort	
Scoring system	**Proportion failed closures**	**C-statistic (95%CI)**	**Proportion failed closures**	**C-statistic (95%CI)**
Tafesse		.67 (0.62-0.72)		.66 (0.61-0.71)
0	23/317 (7.26)		23 / 289 (7.96)	
2	41/244 (16.80)		45 / 262 (17.18)	
3	28 / 75 (37.33)		32 / 85 (37.65)	
WHO		.68 (0.63- 0.74)		.59 (0.54- 0.65)
0	26/379 (6.86)		45 / 372 (12.10)	
2	37/186 (19.89)		32 / 193 (16.58)	

	Derived cohort		Validation cohort	
Scoring system	**Proportion failed closures**	**C-statistic (95%CI)**	**Proportion failed closures**	**C-statistic (95%CI)**
4	29/72 (40.28)		23 / 72 (31.94)	
Proposed		.68 (0.63-0.73)		.63 (0.58-0.69)
0	17/309 (5.50)		27 / 293 (9.22)	
1	3/46(6.52)		13 / 55(23.64)	
2	29/126(23.02)		13 / 127(10.24)	
3	43/156(27.56)		47 / 162 (29.01)	

Figure E.1: ROC curves –derivation cohort, outcome at discharge

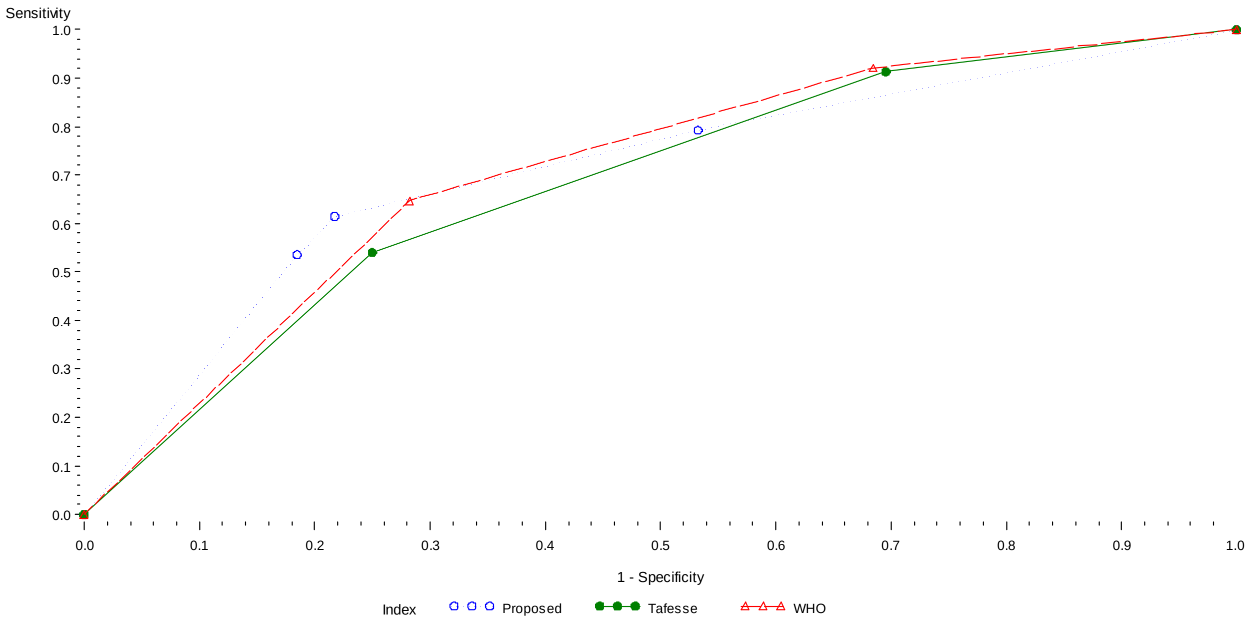
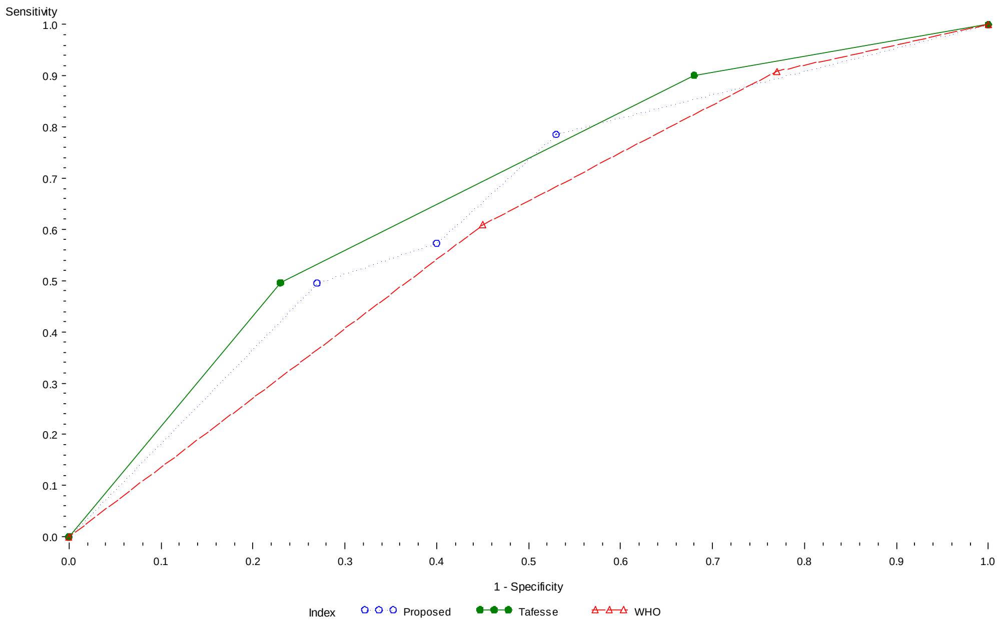


Figure E.2: ROC curves –validation cohort, outcome at discharge


Sensitivity
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0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1 - Specificity
Index
Proposed
Tafesse
WHO

Appendix F: Distribution of success rates, surgeons, and peri-operative procedures across sites

Table F.1: Distribution of success rates, surgeons, and peri-operative procedures across sites

	Site N (%)											
Characteristic	**Total (n=1328)**	**Site A (n=84)**	**Site B (n=48)**	**Site C (n=5)**	**Site D (n=246)**	**Site E (n=72)**	**Site F (n=93)**	**Site G (n=57)**	**Site H (n=208)**	**Site I (n=151)**	**Site J (n=160)**	**Site K (n=204)**
Number of surgeons	51[i]	7	5	2	6	6	4	8	2	5	5	10
Number of patients returning for follow-up visit	1274 (95.93)	71 (84.52)	48 (100.00)	5 (100.00)	246 (100.00)	67 (93.06)	68 (73.12)	53 (92.98)	208 (100.00)	146 (96.69)	159 (99.38)	203 (99.51)
Successful repair at discharge	1104 (84.47)	62 (75.61)	34 (70.83)	5 (100.00)	204 (82.93)	40 (59.70)	72 (86.75)	39 (72.22)	189 (90.87)	115 (76.16)	141 (88.13)	203 (100.00)
Successful repair at follow-up	1039 (81.55)	52 (73.24)	34 (70.83)	3 (60.00)	185 (75.20)	40 (59.70)	45 (66.18)	37 (69.81)	190 (91.35)	117 (80.14)	138 (86.79)	198 (97.54)
Repair conducted in the context of training (n=1314)	485 (36.94)	3 (3.61)	0 (00.00)	0 (00.00)	246 (100.00)	29 (43.28)	38 (42.70)	7 (12.73)	11 (5.29)	7 (4.67)	26 (16.25)	121 (59.90)
Repair part of outreach services / camp (n=1313)	554 (42.16)	0 (00.00)	36 (75.00)	0 (00.00)	246 (100.00)	45 (67.16)	8 (8.99)	17 (30.91)	6 (2.88)	11 (7.33)	21 (13.13)	164 (81.19)
Pre-operative procedures												
Pre-operative antibiotics administered prophylactically (n=1314)	541 (41.17)	48 (57.83)	48 (100.00)	3 (60.00)	246 (100.00)	2 (2.99)	46 (51.69)	4 (7.27)	9 (4.35)	33 (22.00)	28 (17.50)	74 (36.27)
Pre-operative antibiotics administered therapeutically (n=1314)	50 (3.81)	11 (13.25)	0 (00.00)	0 (00.00)	0 (00.00)	0 (00.00)	2 (2.25)	3 (5.45)	9 (4.35)	12 (8.00)	12 (7.50)	1 (0.49)

[i] Number of unique surgeons

	Site N (%)											
Characteristic	**Total (n=1328)**	**Site A (n=84)**	**Site B (n=48)**	**Site C (n=5)**	**Site D (n=246)**	**Site E (n=72)**	**Site F (n=93)**	**Site G (n=57)**	**Site H (n=208)**	**Site I (n=151)**	**Site J (n=160)**	**Site K (n=204)**
Drinking regimen prescribed pre-operatively (n=1311)	1053 (80.32)	33 (39.29)	48 (100.00)	0 (00.00)	246 (100.00)	67 (100.00)	0 (00.00)	29 (51.79)	138 (66.99)	150 (100.00)	158 (100)	187 (92.12)
Median liters of fluid prescribed (IQR) (n=1057)	5 (4-8)	5 (5-5)	4 (4-4)	N/A	4 (3-5)	6 (6-6)	N/A	8 (6-8)	10 (7-10)	8 (8-8)	3 (3-3)	5 (4-5)
Intra-operative procedures												
Vaginal route (n=1273)	1253 (95.29)	71 (85.54)	46 (95.83)	5 (100.00)	238 (96.75)	67 (100.00)	89 (100.00)	53 (96.36)	207 (99.52)	151 (100.00)	133 (83.13)	193 (95.07)
Single layer suture of bladder (n=1271)	820 (64.52)	65 (80.25)	28 (59.57)	5 (100.00)	30 (12.20)	65 (97.01)	26 (32.91)	49 (89.09)	169 (84.08)	92 (61.33)	118 (80.82)	173 (89.18)
Double layer suture of bladder (n=1265)	428 (33.83)	15 (18.99)	19 (40.43)	0 (00.00)	215 (87.40)	1 (1.49)	53 (66.25)	3 (5.56)	17 (8.54)	58 (38.67)	24 (16.55)	23 (11.92)
Single layer suture of vaginal mucosa (n=1269)	1076 (84.79)	73 (90.12)	47 (100.00)	5 (100.00)	244 (99.19)	66 (98.51)	29 (36.71)	44 (80.00)	174 (87.44)	132 (88.00)	120 (82.19)	142 (73.20)
Double layer suture of vaginal mucosa (n=1261)	14 (1.11)	1 (1.27)	0 (00.00)	0 (00.00)	1 (0.41)	0 (00.00)	2 (2.56)	1 (1.85)	1 (0.50)	0 (00.00)	3 (2.07)	5 (2.60)
Martius flap (with or without labia skin) (n=1261)	43 (3.41)	4 (5.06)	6 (12.77)	0 (00.00)	17 (6.91)	0 (00.00)	0 (00.00)	0 (00.00)	15 (7.54)	0 (00.00)	0 (00.00)	1 (0.52)
Relaxing incision (n=1261)	16 (1.27)	0 (00.00)	2 (4.26)	1 (20.00)	0 (00.00)	0 (00.00)	0 (00.00)	3 (5.56)	6 (3.02)	1 (0.67)	0 (00.00)	3 (1.56)
Post-operative procedures												
Open drainage system (n=1309)	899 (68.68)	0 (00.00)	0 (00.00)	1 (20.00	95 (38.62)	67 (100.00)	0 (00.00)	41 (74.55)	203 (100.00)	151 (100.00)	147 (91.88)	194 (95.57)

	Site N (%)											
Characteristic	**Total (n=1328)**	**Site A (n=84)**	**Site B (n=48)**	**Site C (n=5)**	**Site D (n=246)**	**Site E (n=72)**	**Site F (n=93)**	**Site G (n=57)**	**Site H (n=208)**	**Site I (n=151)**	**Site J (n=160)**	**Site K (n=204)**
Median days of catheterization (IQR) (n=1261)	21.00 (14-27)	21.00 (17-21)	14.00 (14-20)	14.00 (14-14)	15.00 (14-21)	28.00 (28-28)	14.00 (13-15)	29.00 (28-34)	23.00 (21-28)	28.00 (28-28)	14.00 (14-21)	15.00 (14-16)
Drinking regimen prescribed post-operatively (n=1304)	1148 (88.04)	60 (74.07)	48 (100.00)	0 (00.00)	246 (100.00)	67 (100.00)	0 (00.00)	7 (12.96)	208 (100.00)	150 (100.00)	160 (100.00)	202 (100.00)
Median liters of fluid prescribed (n=1138)	5 (4-8)	3 (3-5)	4 (4-4)	N/A	3 (3-3)	10 (10-10)	N/A	6 (6-10)	10 (10-10)	8 (8-8)	6 (6-6)	5 (5-5)
Bladder training provided (n=1305)	670 (51.34)	23 (28.40)	7 (14.58)	1 (20.00)	79 (32.11)	44 (65.67)	0 (00.00)	28 (51.85)	13 (6.25)	121 (80.13)	159 (100.00)	195 (96.06)
Prophylactic antibiotics provided (n=1305)	1122 (85.98)	76 (93.83)	3 (6.25)	2 (40.00)	246 (100.00)	64 (96.97)	83 (100.00)	8 (14.81)	208 (100.00)	151 (100.00)	160 (100.00)	124 (61.08)
Bed-rest prescribed > 3 days (n=1328)	244 (18.37)	5 (5.95)	0 (00.00)	2 (40.00)	151 (61.38)	0 (00.00)	38 (40.86)	0 (00.00)	3 (1.44)	0 (00.00)	15 (9.38)	30 (14.71)
Patient did pelvic-muscle exercises (n=1308)	1118 (85.47)	62 (73.81)	12 (25.53)	5 (100.00)	226 (91.87)	48 (72.73)	0 (00.00)	53 (96.36)	202 (97.12)	150 (100.00)	158 (98.75)	202 (100.00)

Appendix G: Propensity score matching for analyses of route of repair and fistula closure

In this appendix, I illustrate the overlap in propensity between participants operated using an abdominal / combined route versus vaginal route of repair. Propensity scores were first calculated using a reduced model comprised of fistula characteristics (abdominal route of repair indicated, mid-vaginal or juxta-cervical location, partial urethral damage or complete damage / transaction of the urethra) only. Since no individuals undergoing abdominal repair had a propensity score <.004, individuals with a propensity score lower than this value were excluded from the analyses. Upon visual examination of p-values and distribution of covariates in Table G.2, it appears that covariate balance is somewhat improved (though imbalance remains in terms of some patient and fistula characteristics, surgeon skill, and procedures). Due to this remaining imbalance, I matched participants on an expanded set of covariates, including fistula characteristics, parity, site, and surgeon skill. Observations with a propensity score <.0029 or >.856 were excluded from the analyses. Covariate balance was further improved, as shown in Table G.4, though some imbalances remained; since a large proportion of the sample had to be excluded from the analyses, no further covariates were included.

Table G.1: Overlap in propensity between participants operated using an abdominal / combined route vs vaginal route, propensity scores calculated using reduced model

Route	Obs	N	Mean	Std Dev	Minimum	Maximum
0	1216	1202	0.0334723	0.0706272	1.3590802E-6	0.6996159
1	57	52	0.2262770	0.1999126	0.0042345	0.6996159

Figure G.1: Overlap in propensity between participants operated using an abdominal / combined route versus vaginal route, propensity scores calculated using reduced model

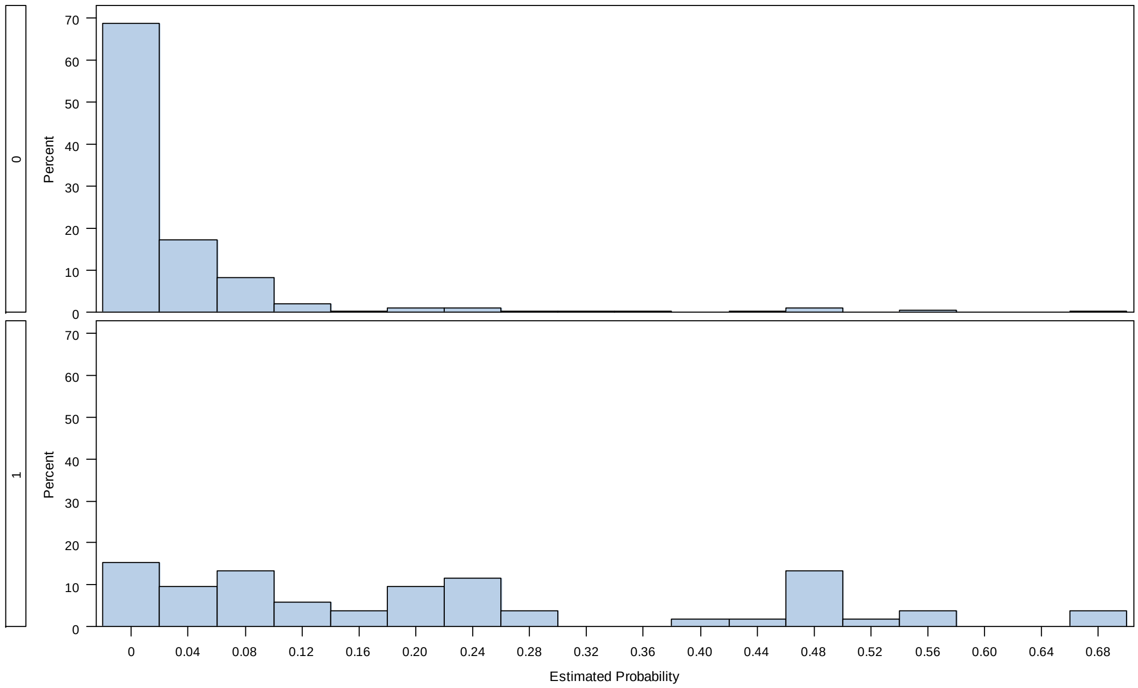
0
1
Percent
Percent
0
10
20
30
40
50
60
70
0
0.04
0.08
0.12
0.16
0.20
0.24
0.28
0.32
0.36
0.40
0.44
0.48
0.52
0.56
0.60
0.64
0.68
Estimated Probability

Table G.2: Assessing balance after matching on propensity for abdominal versus vaginal route of repair (reduced model)

	Total		Abdominal/combined		Vaginal		
	N	(%)	N	(%)	N	(%)	
Total	138	(100)	46	(100)	92	(100)	
Site							
Kumudini	15	(10.9)	9	(19.6)	6	(6.5)	
Lamb	4	(2.9)	2	(4.3)	2	(2.2)	
Kissidougou	36	(26.1)	7	(15.2)	29	(31.5)	
Maradi	5	(3.6)	0	(0.0)	5	(5.4)	
Lamorde	7	(5.1)	0	(0.0)	7	(7.6)	
Sokoto	1	(0.7)	1	(2.2)	0	(0.0)	
Zamfara	13	(9.4)	1	(2.2)	12	(13.0)	
Kebbi	5	(3.6)	0	(0.0)	5	(5.4)	
Kagando	34	(24.6)	20	(43.5)	14	(15.2)	
Kitovu	18	(13.0)	6	(13.0)	12	(13.0)	
Age >25	86	(62.3)	33	(71.7)	53	(57.6)	*
Currently married	86	(62.3)	27	(58.7)	59	(64.1)	
Duration of fistula	4.2	(6.0)	4.8	(6.8)	3.9	(5.6)	
≥ Primary education	36	(26.1)	17	(37.0)	19	(20.7)	*
Rural residence	124	(89.9)	42	(91.3)	82	(89.1)	
Parity >3	63	(47.0)	26	(57.8)	37	(41.6)	*
Average prognostic score	1.43	(1.6)	1.00	(1.4)	1.64	(1.7)	**
Previous repaired	35	(25.4)	12	(26.1)	23	(25.0)	
Any scarring	63	(45.7)	20	(43.5)	43	(46.7)	
> 1 urinary fistula	16	(11.7)	3	(6.5)	13	(14.3)	
Urethral damage							
Partial	22	(16.1)	3	(6.5)	19	(20.9)	**
Transection or complete	16	(11.7)	4	(8.7)	12	(13.2)	
Ureteric involvement	70	(50.7)	23	(50.0)	47	(51.1)	
Small bladder	46	(36.5)	12	(29.3)	34	(40.0)	
Comorbidities at baseline							
Helminthiasis	20	(14.5)	1	(2.2)	19	(20.7)	**
Malnutrition	7	(5.1)	3	(6.5)	4	(4.3)	
Anemia	11	(8.0)	5	(10.9)	6	(6.5)	
Urine dermatitis	4	(6.9)	0	(0.0)	4	(11.8)	*
Fever	0	(0.0)	0	(0.0)	0	(0.0)	*
UTI	0	(0.0)	0	(0.0)	0	(0.0)	
Foot drop	3	(2.2)	0	(0.0)	3	(3.3)	
Fistula location							
Juxta-urethral	3	(2.2)	1	(2.2)	2	(2.2)	
Mid-vaginal	21	(15.2)	3	(6.5)	18	(19.6)	**
Juxta-cervical	13	(9.4)	5	(10.9)	8	(8.7)	
Intra-cervical	16	(11.6)	7	(15.2)	9	(9.8)	

Vesico-uterine	13	(9.4)	4	(8.7)	9	(9.8)	
Circumferential	13	(9.4)	4	(8.7)	9	(9.8)	
Ureteric	10	(7.2)	6	(13.0)	4	(4.3)	*
Trigonal	19	(13.8)	5	(10.9)	14	(15.2)	
Supra-trigonal	15	(10.9)	5	(10.9)	10	(10.9)	
Uretero-vaginal	12	(8.7)	5	(10.9)	7	(7.6)	
Vault	6	(4.3)	2	(4.3)	4	(4.3)	
Surgical procedure							
1-layer bladder suture	65	(50.8)	20	(51.3)	45	(50.6)	
2-layer bladder suture	57	(44.5)	16	(41.0)	41	(46.1)	
1-layer mucosa suture	98	(77.2)	25	(64.1)	73	(83.0)	**
2-layer mucosa suture	3	(2.4)	3	(7.7)	0	(0.0)	**
Relaxing incision	0	(0.0)	0	(0.0)	0	(0.0)	
Martius flap	5	(3.9)	0	(0.0)	5	(5.7)	
Number of complex repairs performed by surgeon							
< 50	56	(42.1)	29	(63.0)	27	(31.0)	**
50-200	48	(36.1)	11	(23.9)	37	(42.5)	**
200-1000	16	(12.0)	5	(10.9)	11	(12.6)	
> 1000	13	(9.8)	1	(2.2)	12	(13.8)	**

Table G.3: Overlap in propensity between participants operated using an abdominal / combined route versus vaginal route, propensity scores calculated using expanded model

Approach	N Obs	N	Mean	Std Dev	Minimum	Maximum
0	1216	1098	0.0274832	0.0709935	2.770879E-10	0.8561966
1	57	51	0.4083025	0.3219966	0.0029727	0.9582981

Figure G.2: Overlap in propensity between participants operated using an abdominal / combined route versus vaginal route, propensity scores calculated using expanded model

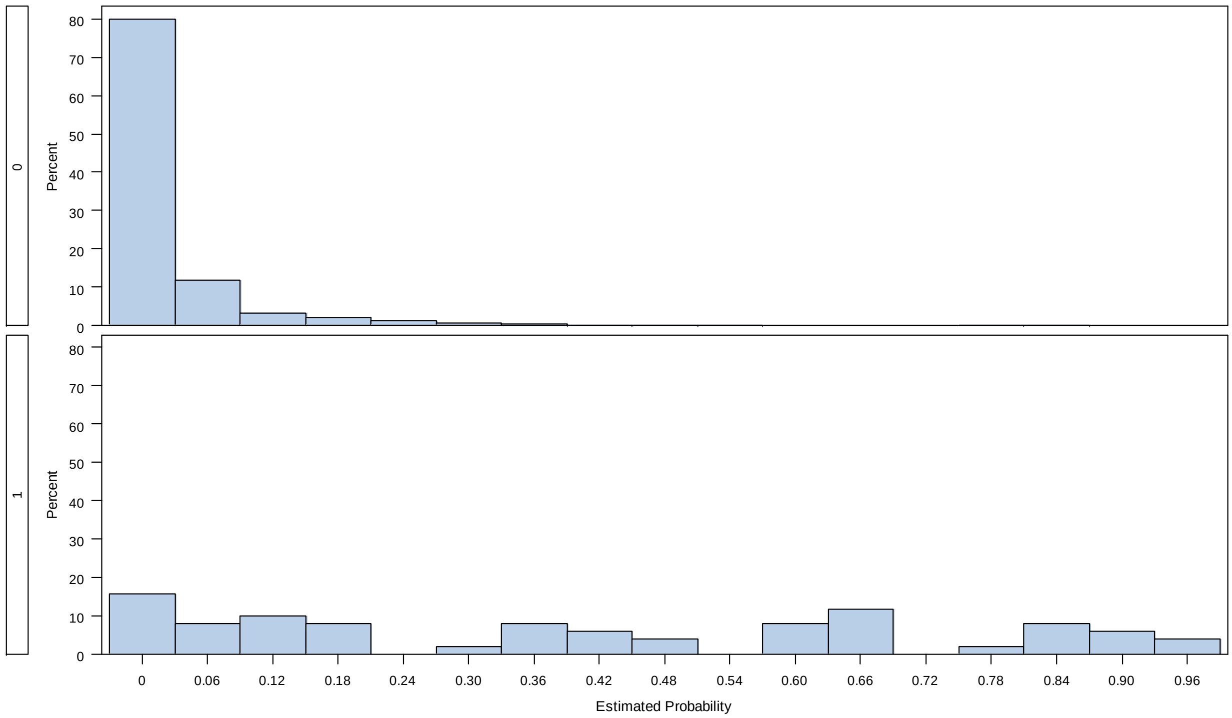
0
Percent
80
70
60
50
40
30
20
10
0
1
Percent
80
70
60
50
40
30
20
10
0
0
0.06
0.12
0.18
0.24
0.30
0.36
0.42
0.48
0.54
0.60
0.66
0.72
0.78
0.84
0.90
0.96
Estimated Probability

Table G.4: Assessing balance after matching on propensity for abdominal versus vaginal route of repair (expanded model)

	Total N	Total (%)	Abdominal/combined N	Abdominal/combined (%)	Vaginal N	Vaginal (%)	
Total	90	(100)	30	(100)	60	(100)	
Site							
Kumudini	17	(18.9)	6	(20.0)	11	(18.3)	
Lamb	4	(4.4)	2	(6.7)	2	(3.3)	
MCH	1	(1.1)	0	(0.0)	1	(1.7)	
Kissidougou	17	(18.9)	8	(26.7)	9	(15.0)	
Sokoto	1	(1.1)	1	(3.3)	0	(0.0)	
Zamfara	2	(2.2)	1	(3.3)	1	(1.7)	
Kebbi	4	(4.4)	0	(0.0)	4	(6.7)	
Kagando	32	(35.6)	7	(23.3)	25	(41.7)	
Kitovu	12	(13.3)	5	(16.7)	7	(11.7)	
Age >25	65	(72.2)	20	(66.7)	45	(75.0)	
Currently married	55	(61.1)	18	(60.0)	37	(61.7)	
Duration of fistula	4.3	(6.3)	6.0	(7.6)	3.5	(5.4)	*
≥ Primary education	23	(25.6)	10	(33.3)	13	(21.7)	
Rural residence	82	(91.1)	26	(86.7)	56	(93.3)	
Parity >3	39	(43.3)	14	(46.7)	25	(41.7)	
Average prognostic score	1.2	(1.4)	1.2	(1.5)	1.3	(1.3)	
Previous repaired	24	(26.7)	10	(33.3)	14	(23.3)	
Any scarring	43	(47.8)	14	(46.7)	29	(48.3)	
> 1 urinary fistula	5	(5.6)	1	(3.3)	4	(6.7)	
Urethral damage							
Partial	9	(10.1)	3	(10.0)	6	(10.2)	
Transection or complete	14	(15.7)	4	(13.3)	10	(16.9)	
Ureteric involvement	31	(34.4)	12	(40.0)	19	(31.7)	
Small bladder	27	(34.6)	11	(40.7)	16	(31.4)	
Comorbidities at baseline							
Helminthiasis	9	(10.0)	2	(6.7)	7	(11.7)	
Malnutrition	12	(13.3)	2	(6.7)	10	(16.7)	
Anemia	12	(13.3)	3	(10.0)	9	(15.0)	
Urine dermatitis	5	(11.6)	0	(0.0)	5	(17.2)	*
Fever	1	(2.3)	0	(0.0)	1	(3.4)	
UTI	0	(0.0)	0	(0.0)	0	(0.0)	
Foot drop	2	(2.2)	0	(0.0)	2	(3.3)	
Fistula location							
Juxta-urethral	12	(13.3)	1	(3.3)	11	(18.3)	*
Mid-vaginal	8	(8.9)	3	(10.0)	5	(8.3)	
Juxta-cervical	13	(14.4)	5	(16.7)	8	(13.3)	
Intra-cervical	14	(15.6)	5	(16.7)	9	(15.0)	
Vesico-uterine	9	(10.0)	3	(10.0)	6	(10.0)	

Circumferential	14	(15.6)	4	(13.3)	10	(16.7)	
Ureteric	2	(2.2)	0	(0.0)	2	(3.3)	
Trigonal	10	(11.1)	4	(13.3)	6	(10.0)	
Supra-trigonal	3	(3.3)	2	(6.7)	1	(1.7)	
Uretero-vaginal	4	(4.4)	2	(6.7)	2	(3.3)	
Vault	9	(10.0)	1	(3.3)	8	(13.3)	
Surgical procedure							
1-layer bladder suture	54	(62.8)	14	(48.3)	40	(70.2)	*
2-layer bladder suture	30	(34.9)	13	(44.8)	17	(29.8)	
1-layer mucosa suture	74	(86.0)	20	(69.0)	54	(94.7)	**
2-layer mucosa suture	3	(3.5)	2	(6.9)	1	(1.8)	
Relaxing incision	0	(0.0)	0	(0.0)	0	(0.0)	
Martius flap	1	(1.2)	0	(0.0)	1	(1.8)	
Number of complex repairs performed by surgeon							
< 50	51	(56.7)	13	(43.3)	38	(63.3)	*
50-200	26	(28.9)	12	(40.0)	14	(23.3)	*
200-1000	6	(6.7)	3	(10.0)	3	(5.0)	
> 1000	7	(7.8)	2	(6.7)	5	(8.3)	

Appendix H: Propensity score matching for analyses of duration of catheterization and fistula closure

In this appendix, I illustrate the overlap in propensity between participants catheterized for > 14 days and ≤ 14 days. Propensity scores for duration of catheterization analyses were first calculated using a reduced model comprised of patient and fistula characteristics, context of repair, as well as intra- and post-operative procedures. Since no individuals catheterized for ≥ 14 days had a propensity score <.038, and no individuals catheterized for < 14 days had a propensity score > .808, individuals with a propensity score lower or higher than those values, respectively, were excluded from the analyses. A comparison of individuals repaired vaginally and abdominally by covariates is shown in Table H.2. To address remaining imbalance in patient and facility-level characteristics, I matched participants on an expanded set of covariates, including site, and surgeon skill. For reasons described above, observations with a propensity score <.006 or >.895 were excluded from the analyses. Covariate balance was further improved, as shown in Table H.4, though some imbalances remained; since a large proportion of the sample had to be excluded from the analyses, no further covariates were included.

Table H.1: Overlap in propensity between participants catheterized <14 days and > 14 days, propensity scores calculated using reduced model

Grp	N Obs	N	Mean	Std Dev	Minimum	Maximum
0	400	362	0.4553530	0.1969103	0.0381696	0.8339966
1	894	774	0.2547317	0.1837855	0.000694828	0.8086595

Figure H.1: Overlap in propensity between participants catheterized <14 days and > 14 days, propensity scores calculated using reduced model

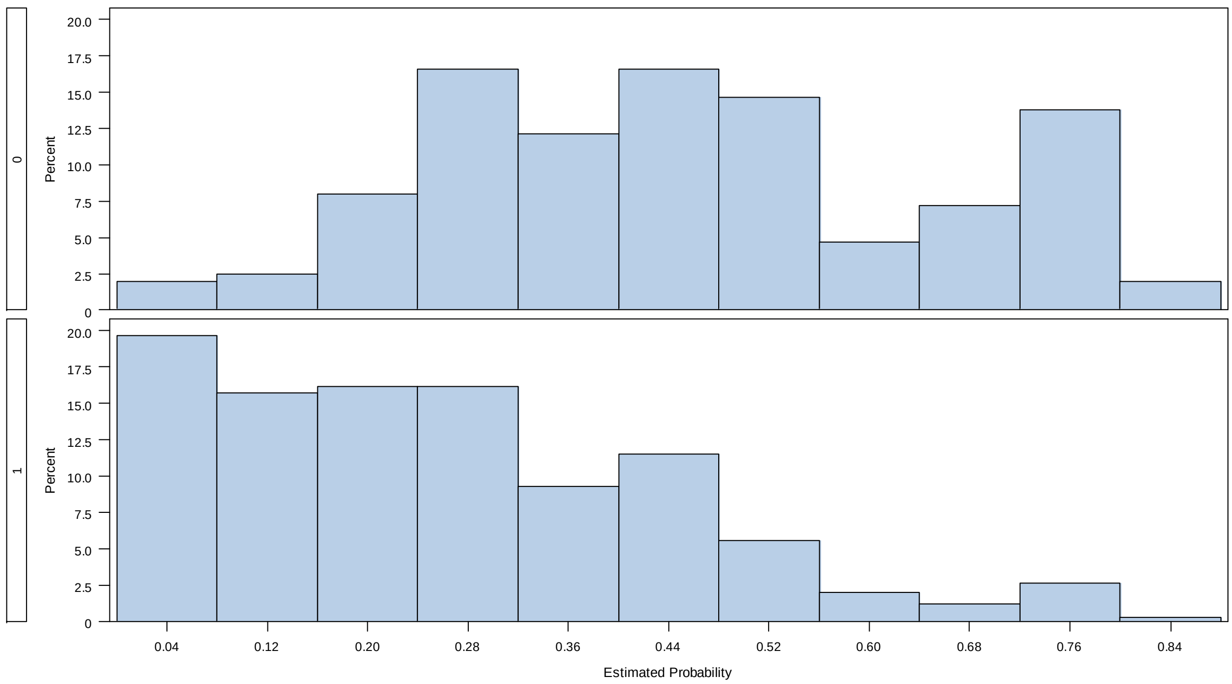
0
1
Percent
Percent
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0
0.04
0.12
0.20
0.28
0.36
0.44
0.52
0.60
0.68
0.76
0.84
Estimated Probability

Table H.2: Patient characteristics by duration of catheterization (matched sample, reduced model)

	Total N	(%)	<14 days N	(%)	>14 days N	(%)	
Total	806	(100)	264	(100)	542	(100)	
Site							
Kumudini	22	(2.7)	2	(0.8)	20	(3.7)	
Lamb	38	(4.7)	21	(8.0)	17	(3.1)	
MCH	4	(0.5)	4	(1.5)	0	(0.0)	
Kissidougou	164	(20.3)	63	(23.9)	101	(18.6)	
Maradi	62	(7.7)	0	(0.0)	62	(11.4)	
Lamorde	47	(5.8)	28	(10.6)	19	(3.5)	
Sokoto	48	(6.0)	0	(0.0)	48	(8.9)	
Zamfara	62	(7.7)	3	(1.1)	59	(10.9)	
Kebbi	86	(10.7)	1	(0.4)	85	(15.7)	
Kagando	120	(14.9)	67	(25.4)	53	(9.8)	
Kitovu	153	(19.0)	75	(28.4)	78	(14.4)	
Age > 25	401	(49.8)	146	(55.3)	255	(47.0)	**
Currently married	520	(64.5)	176	(66.7)	344	(63.5)	
Duration of fistula	3.4	(5.6)	3.7	(5.9)	3.3	(5.5)	
≥ Primary education	179	(22.3)	76	(28.8)	103	(19.1)	**
Rural residence	680	(85.1)	230	(88.1)	450	(83.6)	*
Parity > 3	304	(38.5)	113	(43.3)	191	(36.1)	*
Average prognostic score	1.2	(1.4)	1.1	(1.4)	1.3	(1.4)	*
Previously repaired	199	(24.8)	57	(21.6)	142	(26.3)	*
Any scarring	285	(35.4)	95	(36.0)	190	(35.1)	
> 1 urinary fistula	55	(6.8)	17	(6.5)	38	(7.0)	
Urethral damage							
Partial	207	(25.7)	60	(22.7)	147	(27.1)	*
Transection or complete	116	(14.4)	35	(13.3)	81	(14.9)	
Ureteric involvement	115	(14.3)	41	(15.5)	74	(13.7)	
Small bladder	156	(19.4)	44	(16.7)	112	(20.7)	*
Comorbidities at baseline							
Helminthiasis	92	(11.4)	34	(12.9)	58	(10.7)	
Malnutrition	6	(0.7)	2	(0.8)	4	(0.7)	
Anemia	12	(1.5)	4	(1.5)	8	(1.5)	
Urine dermatitis	26	(11.1)	10	(9.5)	16	(12.3)	
Fever	5	(2.1)	1	(1.0)	4	(3.1)	
UTI	1	(0.1)	1	(0.4)	0	(0.0)	
Foot drop	7	(0.9)	2	(0.8)	5	(0.9)	
Fistula location							
Juxta-urethral	208	(25.8)	63	(23.9)	145	(26.8)	
Mid-vaginal	234	(29.0)	65	(24.6)	169	(31.2)	*
Juxta-cervical	153	(19.0)	58	(22.0)	95	(17.5)	*

Intra-cervical	55	(6.8)	19	(7.2)	36	(6.6)	
Vesico-uterine	17	(2.1)	10	(3.8)	7	(1.3)	**
Circumferential	106	(13.2)	33	(12.5)	73	(13.5)	
Ureteric	11	(1.4)	6	(2.3)	5	(0.9)	*
Trigonal	41	(5.1)	15	(5.7)	26	(4.8)	
Supra-trigonal	26	(3.2)	18	(6.8)	8	(1.5)	**
Uretero-vaginal	8	(1.0)	3	(1.1)	5	(0.9)	
Vault	20	(2.5)	12	(4.5)	8	(1.5)	**
Surgical procedure							
Vaginal route	772	(95.8)	245	(92.8)	527	(97.2)	**
1-layer bladder suture	519	(64.4)	164	(62.1)	355	(65.5)	
2-layer bladder suture	280	(34.7)	98	(37.1)	182	(33.6)	
1-layer mucosa suture	681	(84.5)	205	(77.7)	476	(87.8)	**
2-layer mucosa suture	11	(1.4)	4	(1.5)	7	(1.3)	
Relaxing incision	9	(1.1)	4	(1.5)	5	(0.9)	
Martius flap	8	(1.0)	3	(1.1)	5	(0.9)	
Post-operative procedures administered							
Open catheter drainage	584	(72.5)	181	(68.6)	403	(74.4)	*
Drinking regimen	700	(87.0)	231	(87.5)	469	(86.7)	
Bladder training	487	(60.4)	171	(64.8)	316	(58.3)	*
Prophy. antibiotics	666	(82.6)	211	(79.9)	455	(83.9)	*
>1 day vaginal pack	268	(33.3)	107	(40.5)	161	(29.7)	**
Number of complex repairs performed by surgeon							
< 50	300	(39.6)	105	(41.8)	195	(38.5)	
50-200	236	(31.1)	80	(31.9)	156	(30.8)	
200-1000	105	(13.9)	35	(13.9)	70	(13.8)	
> 1000	117	(15.4)	31	(12.4)	86	(17.0)	*

Table H.3: Overlap in propensity between participants catheterized <14 days and > 14 days, propensity scores calculated using expanded model

Grp	N Obs	N	Mean	Std Dev	Minimum	Maximum
0	400	358	0.6010320	0.1725217	0.0064263	0.8959554
1	894	748	0.1909501	0.2514202	0.000137157	0.9025091

Figure H.2: Overlap in propensity between participants catheterized <14 days and > 14 days, propensity scores calculated using expanded model

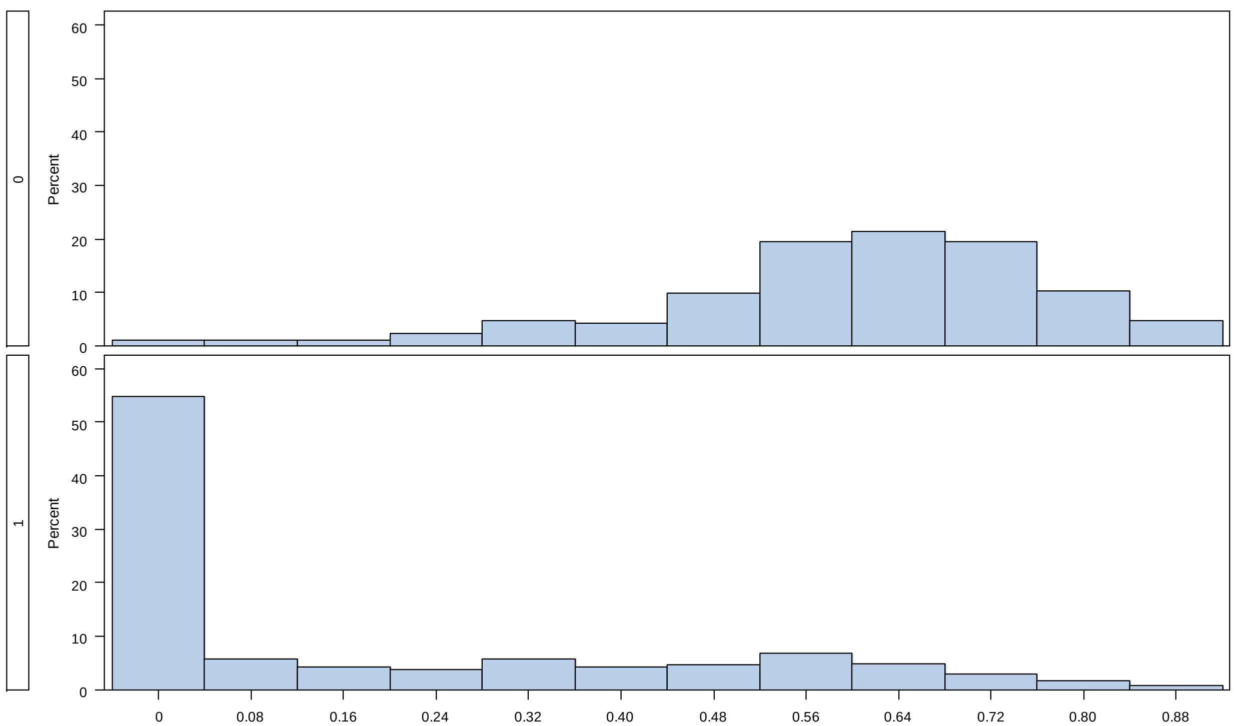

Table H.4: Patient characteristics by duration of catheterization (matched sample, expanded model)

	Total N	(%)	<14 days N	(%)	>14 days N	(%)	
Total	440	(100)	143	(100)	297	(100)	*
Site							
Kumudini	4	(0.9)	2	(1.4)	2	(0.7)	
Lamb	28	(6.4)	11	(7.7)	17	(5.7)	
MCH	4	(0.9)	4	(2.8)	0	(0.0)	
Kissidougou	149	(33.9)	45	(31.5)	104	(35.0)	
Lamorde	38	(8.6)	20	(14.0)	18	(6.1)	
Zamfara	15	(3.4)	2	(1.4)	13	(4.4)	
Kebbi	2	(0.5)	1	(0.7)	1	(0.3)	
Kagando	90	(20.5)	26	(18.2)	64	(21.5)	
Kitovu	110	(25.0)	32	(22.4)	78	(26.3)	
Age > 25	258	(58.6)	94	(65.7)	164	(55.2)	**
Currently married	263	(59.8)	96	(67.1)	167	(56.2)	**
Duration of fistula	4.1	(6.3)	4.3	(6.3)	4.0	(6.3)	
≥ Primary education	124	(28.2)	36	(25.2)	88	(29.7)	
Rural residence	388	(89.0)	124	(87.9)	264	(89.5)	
Parity > 3	177	(40.2)	69	(48.3)	108	(36.4)	**
Average prognostic score	1.5	(1.5)	1.4	(1.6)	1.5	(1.4)	
Previously repaired	109	(24.8)	45	(31.5)	64	(21.5)	**
Any scarring	201	(45.8)	62	(43.4)	139	(47.0)	
> 1 urinary fistula	39	(8.9)	14	(9.8)	25	(8.4)	
Urethral damage							
Partial	105	(23.9)	32	(22.4)	73	(24.6)	
Transection or complete	92	(20.9)	21	(14.7)	71	(23.9)	**
Ureteric involvement	97	(22.0)	33	(23.1)	64	(21.5)	
Small bladder	129	(29.3)	36	(25.2)	93	(31.3)	
Comorbidities at baseline							
Helminthiasis	79	(18.0)	20	(14.0)	59	(19.9)	*
Malnutrition	4	(0.9)	1	(0.7)	3	(1.0)	
Anemia	8	(1.8)	2	(1.4)	6	(2.0)	
Urine dermatitis	10	(6.2)	5	(9.4)	5	(4.6)	
Fever	2	(1.2)	2	(3.7)	0	(0.0)	*
UTI	1	(0.2)	1	(0.7)	0	(0.0)	
Foot drop	3	(0.7)	1	(0.7)	2	(0.7)	
Fistula location							
Juxta-urethral	95	(21.6)	34	(23.8)	61	(20.5)	
Mid-vaginal	95	(21.6)	28	(19.6)	67	(22.6)	
Juxta-cervical	88	(20.0)	31	(21.7)	57	(19.2)	
Intra-cervical	43	(9.8)	12	(8.4)	31	(10.4)	
Vesico-uterine	14	(3.2)	8	(5.6)	6	(2.0)	*

Circumferential	89	(20.2)	19	(13.3)	70	(23.6)	**
Ureteric	5	(1.1)	3	(2.1)	2	(0.7)	
Trigonal	34	(7.7)	9	(6.3)	25	(8.4)	
Supra-trigonal	17	(3.9)	9	(6.3)	8	(2.7)	*
Uretero-vaginal	6	(1.4)	3	(2.1)	3	(1.0)	
Vault	18	(4.1)	9	(6.3)	9	(3.0)	*
Surgical procedure							
Vaginal route	414	(94.1)	130	(90.9)	284	(95.6)	*
1-layer bladder suture	232	(52.7)	76	(53.1)	156	(52.5)	
2-layer bladder suture	203	(46.1)	65	(45.5)	138	(46.5)	
1-layer mucosa suture	361	(82.0)	109	(76.2)	252	(84.8)	**
2-layer mucosa suture	9	(2.0)	3	(2.1)	6	(2.0)	
Relaxing incision	4	(0.9)	2	(1.4)	2	(0.7)	
Martius flap	9	(2.0)	3	(2.1)	6	(2.0)	
Post-operative procedures administered							
Open catheter drainage	269	(61.1)	80	(55.9)	189	(63.6)	*
Drinking regimen	396	(90.2)	118	(82.5)	278	(93.9)	**
Bladder training	255	(58.0)	77	(53.8)	178	(59.9)	
Prophy. antibiotics	372	(84.5)	119	(83.2)	253	(85.2)	
>1 day vaginal pack	231	(52.5)	72	(50.3)	159	(53.5)	
Number of complex repairs							
< 50	129	(30.2)	46	(33.3)	83	(28.7)	
50-200	167	(39.1)	55	(39.9)	112	(38.8)	
200-1000	51	(11.9)	18	(13.0)	33	(11.4)	
> 1000	80	(18.7)	19	(13.8)	61	(21.1)	*

Appendix I: Analyses conducted to test effect modification

In this appendix, I show additional analyses conducted to support evaluation of effect modification by fistula prognosis. First, I calculated the Youden index, a measure of the optimal threshold based on the balance between true and false positives. Based on these calculations (Table I.1), the optimal measure threshold is a score of 3. However, in my primary analyses I chose to use a threshold of 1, corresponding to the median percentile distribution of patients, and favoring increased sensitivity over specificity. In Table I.2, I evaluate the influence of vaginal route of repair on repair outcomes stratified by prognosis of repair. While confidence intervals are overlapping, these analyses suggest that among women with a prognostic score ≥1, vaginal route of repair may be less associated with failure to close the fistula compared to the risk of vaginal route of repair among women with a low prognostic score.

Table I.1: Calculation of Youden index to determine optimal threshold for measure of complexity

Score	Not closed	Closed	Sensitivity	Specificity	Youden
0	32	239	1	0	0
1	16	61	0.862661	0.229587	0.092248
2	24	123	0.793991	0.288184	0.082176
3	**43**	**99**	**0.690987**	**0.40634**	**0.097327**
	233	1041			

Table I.2: The influence of vaginal route of repair on repair outcome across levels of repair prognosis in the unmatched sample

	Prognostic score <1		**Prognostic score ≥1**	
	Closed	Not closed	Closed	Not closed
Vaginal route of repair	462 (93.90)	55 (98.21)	527 (96.17)	172 (97.18)
Abdominal / combined abdominal vaginal	30 (6.10)	1 (1.79)	21 (3.83)	5 (2.82)
RR (95%CI)	1.82 (0.66-5.00)		1.18 (0.67-2.06)	

Appendix J: Predictors of route of repair, and the influence of route of repair on fistula closure, excluding mixed vaginal and abdominal routes of repair

In this appendix, I evaluated whether excluding repairs that were conducted both vaginally and abdominally introduced any bias in the results. I first evaluated whether predictors of abdominal-only route of repair varied from the predictors of abdominal-only or combined abdominal and vaginal route of repair. These analyses had less power than the previous analyses, and it was not possible to adjust for site, due to zero cell-counts. Nonetheless, with the exception of fistula size greater than or equal to 4, which was significant only in the analyses excluding combined route of repair, predictors of abdominal-only route of repair were similar to those of abdominal-only or combined route of repair. In terms of the influence of route of repair on repair outcome, results of the analyses excluding combined route of repair demonstrated a stronger role of vaginal route of repair in predicting repair failure, even after controlling for other factors. The smaller sample size for these analyses may have resulted in unstable estimates; however, these results indicate that while fistulas repaired using a combined approach may be different compared to fistulas repaired using an abdominal approach with regard to repair outcome, the increased risk of vaginal compared to abdominal repair on repair failure is not an artifact of this difference.

Table J.1: Predictors of vaginal versus abdominal route of repair, excluding mixed vaginal and abdominal route of repair

	Abdominal / combined N (%)	Vaginal N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Total (n=1273)	47	1216		
Patient characteristics at baseline				
Parity > 3	28 (62.2)	410 (34.9)	2.94 (1.63-5.31) **	1.80 (0.90-3.60)*
Age > 25	33 (70.2)	566 (46.5)	2.61 (1.41-4.83) **	--
Currently married	33 (70.2)	793 (65.2)	1.25 (0.67-2.31)	
Rural residence	43 (91.5)	1035 (85.8)	1.75 (0.63-4.80)	
> Primary education	13 (27.7)	246 (20.3)	1.48 (0.79-2.76) **	1.13 (0.52-2.44)
Mean years with fistula (sd)	3.1 (5.8)	3.2 (5.4)	1.00 (0.94-1.05)	
Malnutrition	2 (4.3)	72 (5.9)	0.71 (0.18-2.89)	

Anemia	3 (6.4)	84 (6.9)	0.92 (0.29-2.91)	
Fever	0 (0.0)	20 (4.7)	--	
UTI	0 (0.0)	2 (0.2)	--	
Footdrop	0 (0.0)	64 (5.3)	--	
Female genital infibulation	6 (12.8)	40 (7.8)	1.75 (0.76-4.02)	
Prior repair	12 (25.5)	281 (23.2)	1.13 (0.60-2.15)	
Fistula characteristics				
Abdominal repair indicated[i]	43 (91.5)	447 (37.2)	16.63 (6.01-46.04)	14.22 (3.98-50.84)**
Fistula size ≥ 4 cm	3 (7.1)	248 (21.3)	0.29 (0.09-0.94)**	0.20 (0.04-0.87)**
Small bladder	10 (23.3)	326 (28.8)	0.76 (0.38-1.51)	
Extensive scarring	2 (4.3)	93 (7.7)	0.55 (0.13-2.21)	
Extensive tissue loss	4 (9.5)	127 (10.5)	0.90 (0.33-2.49)	
Extent of urethral damage				
No damage	40 (88.9)	710 (58.5)	Ref	Ref
Partial damage	1 (2.2)	278 (22.9)	0.07 (0.01-0.50) **	0.16 (0.02-1.23)*
Complete transection or destruction	4 (9.1)	222 (18.4)	0.34 (0.12-0.94)**	0.70 (0.19-2.52)
Mid-vaginal location	2 (4.3)	366 (30.2)	0.11 (0.03- 0.45)**	0.32 (0.07-1.46)*
Trigonal location	6 (12.8)	60 (5.0)	2.63 (1.16-5.98)**	
Supratrigonal location	6 (12.8)	25 (2.1)	5.77 (2.65-12.57)**	
Juxta-cervical location	3 (6.5)	219 (18.2)	0.32 (0.10-1.03)*	0.61 (0.17-2.10)
Intracervical location	6 (13.0)	74 (6.1)	2.20 (0.96-5.02)*	
Vesico-uterine location	10 (21.7)	11 (0.9)	16.28 (9.37-28.28)**	
Vault location	2 (4.3)	32 (2.7)	1.59 (0.40-6.30)	
Ureter involvement	21 (44.7)	183 (15.2)	4.15 (2.38-7.23)**	
Other abdominal pathology	1 (2.1)	1 (0.1)	13.71 (3.33-56.40)**	
Facility level factors / characteristics				
Site				
A (n=70)	4 (8.5)	61 (87.1)	11.13 (4.30-28.80)**	
B and C (n=53)	0 (0.0)	51 (96.2)	11.82 (4.51-31.01)	
D (n=246)	8 (17.0)	238 (96.8)	9.97 (4.08-24.33)	
E, G, and I (n=266)	1 (2.1)	265 (99.6)	10.88 (4.48-26.43)**	
F and H (n=276)	1 (2.1)	275 (99.6)	5.97 (2.40-14.84) **	
J (n=159)	25 (53.2)	133 (83.7)	4.83 (1.85-12.66)**	
K (n=203)	8 (17.0)	193 (95.1)	Ref	
Surgeon performed over 200 complex repairs	6 (12.8)	404 (35.0)	0.28 (0.12-0.65)**	0.42 (0.13-1.35)*

*p-value<.20
**p-value<.05

Table J.2: Association between vaginal route of repair and failure to close the fistula at three month follow-up visit, excluding combined vaginal and abdominal route of repair

	Not closed	Closed	RR (95% CI)	ARR (95% CI)[ii]	ARR (95% CI)[iii]
Vaginal route	227 (98.3)	989 (95.8)	2.19 (0.85-5.64)	2.75 (1.06-7.11)	2.89 (1.12-7.46)

[i] Female genital infibulation, extensive scarring, extensive tissue loss, trigonal, supratrigonal, intracervical, vesico-uterine location, ureter involvement or concomitant abdominal pathology
[ii] Adjusted for indication for abdominal route of repair
[iii] Adjusted for indication for abdominal route of repair, surgeon experience conducting complex repairs, mid-vaginal location