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RISK FACTORS OF URETHRAL STRICTURE: A SYSTEMATIC REVIEW

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Abstract

Background: *Urethral stricture in males is a narrowing of the anterior urethra caused by fibrosis and cicatrisation of the urethral mucosa and adjacent spongiosus tissue ("spongiofibrosis"). In the male posterior urethra, there is no spongiosus tissue; therefore, stenosis is the preferred term. Understanding the risk factors of urethral strictures may be amenable to preventive measures resulting in a decrease in disease severity and health care expenditure.*

Aim: *This study aims to summarize and assess the risk factors of urethral stricture through a comprehensive systematic review.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (PubMed, Cochrane Library, Google Scholar) and included articles published between 2013–2023. Duplicate publications, review articles, and incomplete articles were excluded.*

Results: *The databases search identified a total of 16.645 articles (Table 1) and resulted in 16.155 articles after duplicates removed. Of these, 15.955 articles were excluded due to non-original study and titles and abstract not represented the focus of interest; and resulting in 200 articles for screening process. Articles not evaluating the focus of interest and articles in which full-text are not available are excluded, resulting in 15 articles for eligibility criteria. Among them, 10 articles did not give sufficient details about the risk factors of urethral stricture and some did nit differenriate clearly between the risk factors of urethral stricture and recurrence of urethral stricture. Hence, we found 5 appropriate studies included.*

Conclusion: *The risk factors of urethral stricture in this study includes the dose of brachyterapy for prostate cancer patients, lower resection speed of BPH, prolonged operative time, intraoperative urethral mucosa rupture, post-operative continuous infection, the diameter of the instrument, presence of chronic prostatitis in anamnesis, increased volume of the prostate, repeated drainage of the bladder using the urethral catheter, high comorbidity burden, second TURP surgery, history of preoperative catheter insertion, high postoperative WBC, and long postoperative catheterization time.*

Keywords: *Risk factor, Predicting factor, Urethral stricture*

INTRODUCTION

Urethral stricture in males is a narrowing of the anterior urethra caused by fibrosis and cicatrisation of the urethral mucosa and adjacent spongiosus tissue ("spongiofibrosis"). In the male posterior urethra, there is no spongiosus tissue; therefore, stenosis is the preferred term.[1] Males experience a significant increase in incidence after 55 years of age, with a mean age of 45,1.[2,3] The incidence is estimated to range between 229 and 627 per 100,000 males.[3] Most commonly afflicted is the anterior urethra (92,2%), specifically the bulbar urethra (46%).[2]

Due to disparities in healthcare quality, environment, and practice patterns, the etiology of sprains and strains varies considerably across the globe's various regions.[4] The most prevalent cause of urethral stricture in developed nations is idiopathic, followed by iatrogenic. Common iatrogenic causes include late failure of hypospadias surgery and stricture resulting from endoscopic manipulation (e.g. transurethral resection). In contrast, trauma is the leading cause of death in developing nations, reflecting higher rates of road traffic injuries, less developed trauma systems, inadequate road infrastructure, and possibly socioeconomic factors.[5]

Depending on the severity of the hypospadias and the technique used, urethral strictures are reported in 1.3% to 20% of cases following hypospadias repair. Due to a higher rate of surgical repair, the incidence of this type of strictures is substantially higher in countries with ample resources.[4] Up to 18% of all urethral strictures have been reported to involve the meatus or fossa navicularis, most commonly as a result of failed hypospadias repair (FHR), lichen sclerosus (LS), trauma/instrumentation, or idiopathic causes.[6,7] Meatal stenosis after circumcision has been reported in less than 0.2% of neonates who undergo circumcision.[3]

After radiation therapy for prostate cancer, urethral stricture is a late complication typically observed 1–3 years later. The incidence of urethral stricture following radiation therapy for prostate cancer varies between 0% and 18%. Approximately 2% of patients undergoing external beam (EBRT), 4% for brachytherapy (BT), and 11% for EBRT-BT combination therapy develop urethral stricture. Several risk factors for urethral stricture development have been identified. Prior transurethral resection of the prostate (TURP) raises stricture rates to as high as 15%, compared to 6% in the absence of prior resection. History of arterial hypertension in conjunction with diabetes mellitus is also a predictive factor, as this may result in decreased blood supply due to microcirculatory alterations.[8]

The incidence of urethral stricture following transurethral prostate surgery ranges from 4.5 to 13%.[9] The most prevalent cause of iatrogenic urethral stricture, accounting for 41% of all causes[10], is transurethral surgery. The bulbomembranous urethra is the most common site for urethral stricture, followed by the fossa navicularis and penile urethra.[11] Postulated mechanisms include friction at the penoscrotal junction, lack of adequate lubrication, repetitive 'in and out' movement of the resectoscope, compromise of mucosal integrity resulting in urine extravasation, and monopolar current leak due to inadequate resectoscope insulation.[12] Bladder neck stenosis may be caused by excessive and/or circumferential resection, as well as the use of relatively large resection loops, which may generate excessive heat in small intraurethral adenomas, resulting in fibrosis.[13] Stenoses of the posterior urethra may also be caused by a protracted period of inability to void following surgery.[14]

Understanding the risk factors of urethral strictures may be amenable to preventive measures resulting in a decrease in disease severity and health care expenditure. This article provides a systematic review of the risk factors of urethral stricture disease.

Method

Search Strategy

This study is a qualitative systematic review. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar. The keywords used are “Risk Factors” OR “Predictor” AND “Urethral Stricture”. The selected articles are based on inclusion and exclusion criteria.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	“Risk Factors” OR “Predictor” AND “Urethral Stricture”	219
Cochrane Library	“Risk Factors” OR “Predictor” AND “Urethral Stricture”	26
Google Scholar	“Risk Factors” OR “Predictor” AND “Urethral Stricture”	16.400

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were: (1) original articles (observational studies including cohort, case control, cross-sectional); (2) published in the last ten years (2013–2023); (3) full-text articles available; and (4) published in English, and (5) evaluating the risk factors of urethral stricture in males. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not evaluate the focus of interest of this study. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, complete access was gained to all potentially eligible studies. Finally, the systematic review included only those studies that met our inclusion criteria. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guideline is used for the selection.

Data Extraction and Parameter Measured

All the authors extracted the data from the articles. The following datas regarding the risk factors of urethral stricture are collected: Author, year of publication, study design, sample size, study population, age of patients, and risk factors of urethral stricture. All disagreements regarding the methodology, article retrieval, and statistical analysis were resolved by consensus among the authors.

Risk of Bias in Individual Studies

The quality of each study's methodology was determined by the manner in which patients were assigned to the study's arms, the confidentiality of allocation procedures, the use of blinding, and the amount of data lost due to attrition. The studies were then qualitatively classified in accordance with the 2019 Cochrane Handbook for Systematic Reviews of Interventions guidelines. Each study was designated to one of the three following categories based on the quality assessment criteria: A: if all quality criteria were adequately met, the study was judged to have a low risk of bias; B: if one or more quality criteria was only partially met or unclear, the study was judged to have a moderate risk of bias; and C: if one or more criteria were not met, or not included, the study was judged to have a high risk of bias.

Results

The databases search identified a total of 16.645 articles (Table 1) and resulted in 16.155 articles after duplicates removed. Of these, 15.955 articles were excluded due to non-original study and titles and abstract not represented the focus of interest; and resulting in 200 articles for screening process. Articles not evaluating the focus of interest and articles in which full-text are not available are excluded, resulting in 15 articles for eligibility criteria. Among them, 10 articles did not give sufficient details about the risk factors of urethral stricture and some did nit differenriate clearly between the risk factors of urethral stricture and recurrence of urethral stricture. Hence, we found 5 appropriate studies included (Figure 1). The summary of the main findings of the selected studies is presented in Table 2 and 3.

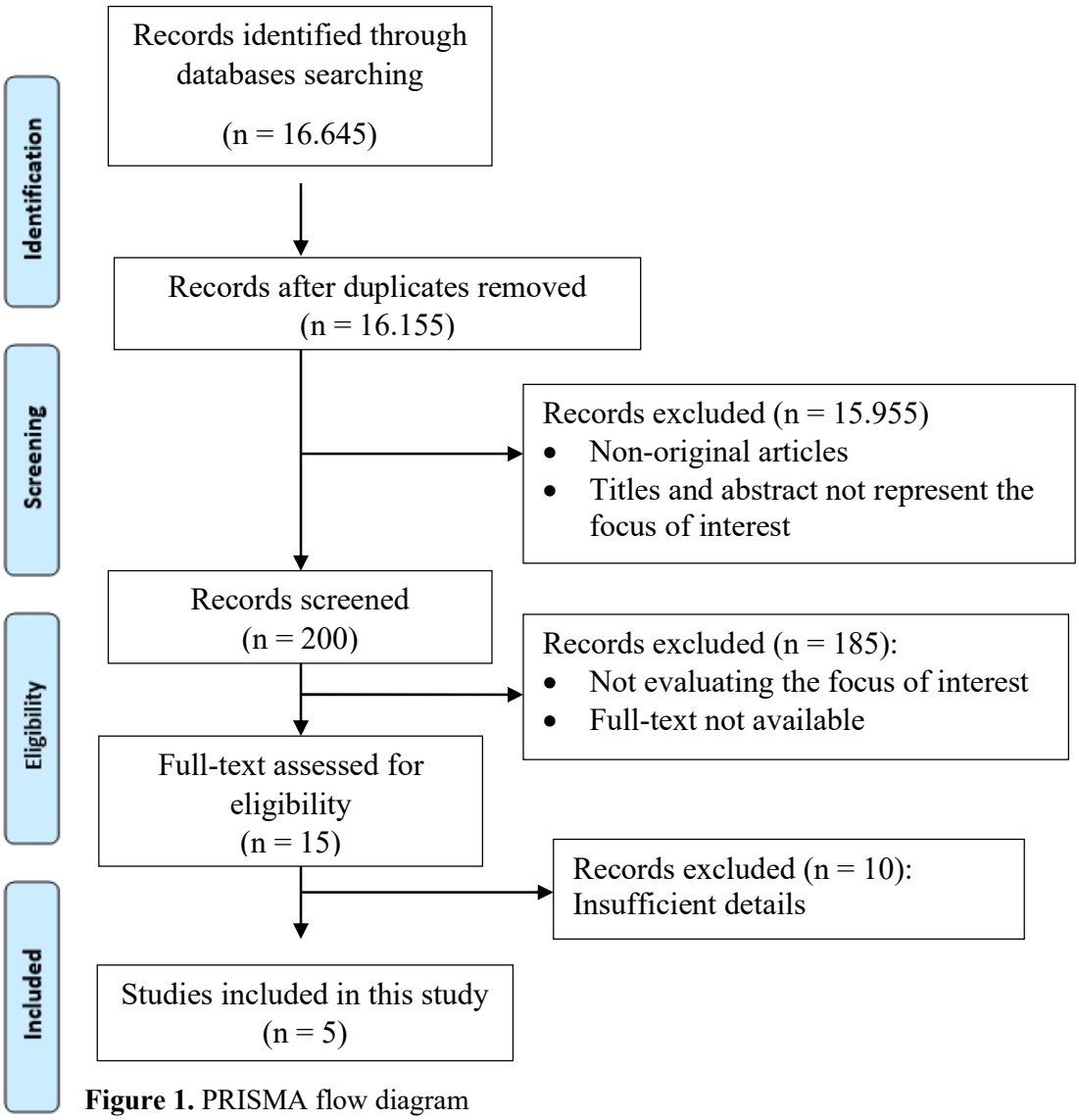

Figure 1. PRISMA flow diagram

Table 2. Characteristics of studies evaluating the risk factors of urethral stricture

Author & year of publication	Study design	Sample size	Study population	Age	Risk factors of urethral stricture
Hindson et al. (2013)[15]	Retrospective cohort	354	Patients with prostate cancer	Mean 65 (46–84)	• Multivariate analysis: the dose of brachyterapy (19 Gy/2) • Univariate analysis: the dose of brachyterapy (19 Gy/2), urologist, radiation oncologist, failed trial of void, implant year, and BED.
Tao et al. (2016)[16]	Retrospective cohort	373	Patients underwent TURP for LUTS suggestive of benign prostatic obstruction (LUTS/BPO)	Mean: 64.1±6.4	Lower resection speed, intraoperative urethral mucosa rupture and post-operative continuous infection.
Grechenkov et al. (2018)[17]	Case control	402	Patients underwent monopolar TURP for BPH.	Mean age: Non-US group: 69 (53–80) US group: 70 (55–80)	The diameter of the instrument, presence of chronic prostatitis in anamnesis, increased volume of the prostate, and repeated drainage of the bladder using the urethral catheter.
Gür et al. (2021)[18]	Case control	3069	Patients underwent TURP for BPH.	Mean age ± SD: Non-US group: 67.88 ± 5.75 US group: Group 66.64 ± 6.75	Prolonged operative time and high comorbidity burden.
Afandiyev & Ugurlu (2022)[19]	Case control	124	Patients underwent BTURP for BPH.	Mean age ± SD: Non-US group: 70.76±8.65 US group: 74.46±8.7	Second TURP surgery, history of preoperative catheter insertion, high postoperative WBC, and long postoperative catheterization time.

BED: Biologic equivalent dose; BPO: Benign prostatic obstruction; BTURP: Bipolar transurethral resection of the prostate; LUTS: Lower urinary tract symptoms; TURP: Transurethral resection of the prostate; WBC: White blood cell count.

Discussion

In this study, we only found five studies published in the last ten years that specifically asses the risk factors of urethral stricture. Among five studies included, four studies were conducted in BPH/LUTS patients and one study conducted among prostate cancer patients. The risk factors of urethral stricture in this study includes the dose of brachyterapy for prostate cancer patients, lower resection speed of BPH, prolonged operative time, intraoperative urethral mucosa rupture, post-operative continuous infection, the diameter of the instrument, presence of chronic prostatitis in anamnesis, increased volume of the prostate, repeated drainage of the bladder using the urethral catheter, high comorbidity burden, second TURP surgery, history of preoperative catheter insertion, high postoperative WBC, and long postoperative catheterization time.

Urethral stricture is a known late effect of any treatment for prostate cancer.[20] It appears that stricture rates are higher in HDRB compared to low-dose-rate brachytherapy (LDRB) and external beam radiation therapy (EBRT), which may indicate a BED response.[21] Mohammed et al.[21] analyzed 1903 patients who were treated with EBRT, LDRB, or HDRB. The risk of stricture was considerably higher in HDRB patients than in EBRT and LDRB patients, 11% versus 2% and 4%, respectively.[15]

LUTS/BPO is prevalent in the elderly male population. Since the 1970s, transurethral resection of the prostate (TURP) has been the most common treatment for symptoms of benign prostatic obstruction (LUTS/BPO) in the lower urinary tract. In recent years, novel endourologic procedures have been implemented and shown to be safe and effective by relevant randomized controlled trials (RCT).[22–24] However, TURP remains the most common surgical procedure in developing nations.

There may be intraoperative and postoperative complications associated with TURP. The majority (2.0% to 21.2%) of intraoperative complications involve bleeding from the resection area. 2.5%–14% of patients experience inflammatory diseases of the urinary tract in the immediate postoperative period. In the long-term period, urethral stricture (2.2%–

9.8%) and/or cicatricial deformity of the bladder neck (0.3%–9.8%) predominate.[17] Failure to void is an important postoperative long-term complication that is frequently caused by urethral stricture or bladder neck contracture (BNC). In prior research, the urethral stricture rate ranges from 2.2% to 9.8%, while the BNC rate ranges from 0.3% to 9.8%.[12] Meatal strictures are typically caused by a mismatch between the size of the instrument and the diameter of the urethral meatus, whereas bulbar strictures result from insufficient isolation of the monopolar current by the lubricant.[15] Increased endoscopic diameter correlates with the risk of sclerotic and cicatricial urethral changes. This may be due to the endoscope's tube wall's compressive effect on corpus spongiosum, which causes ischemia and traumatization of tissues.[17]

Gür et al.[18] looked at the long-term outcomes of urethral stricture cases that developed following TURP surgery in a single center. According to the findings, urethral stricture is likely to occur in roughly 4% of patients after TURP after a minimum of a 12-month follow-up period. Furthermore, logistic regression analysis revealed that the length of the operating duration and the number of comorbidities were effective factors in the formation of urethral stricture after TURP.

According to the literature, prolonged operation duration plays a significant influence in the etiology of urethral stricture after TURP.[25] This can be explained by the use of larger diameter endoscopes with irrigation qualities in significant numbers of prostate patients. As a result of the bigger diameter of the tool, surgery duration was reduced while damage and ischemia of the mucosa and corpus spongiosum increased. As a result, the diameter of the resectoscope affects the chance of developing urethral strictures more than the duration of operation.[17]

The most well-known comorbidity associated with urethral stricture after TURP is diabetes mellitus (DM).[26,27] Similarly, Grechenkov et al.[26] and Kumsar et al.[27] reported that inadequate glycemic control increases the risk of developing urethral stricture in the early postoperative period. In contrast, Gür et al.[18] included patients with other common comorbidities (asthma, COPD, CAD, and hypertension) that could cause tissue ischemia and blood supply disorders and revealed that the risk of early urethral stricture after TURP increased as the patient's comorbidity burden increased.

Although BTURP is an effective procedure, it is also associated with complications such as urethral stricture.[28] The rate of urethral stricture development following BTURP was 10.5%, according to Afandiyev & Ugurlu.[19] In their study, Sarier et al. found that renal transplantation did not increase the risk of urethral stricture and that the incidence of urethral stricture development following BTURP ranged from 8.9 to 12.5%.[29,30] Several studies, the rate of stricture following BTURP ranges between 2% and 12.7%.[31,32] According to Afandiyev & Ugurlu.[19], the median ages of individuals with and without urethral stricture were comparable. Age has been shown to have no statistically significant effect on the development of urethral stricture in numerous studies.

There are several limitations of this study. First, we only found a limited number of articles, with only five studies included. Second, due to the limited number of studies included, there is homogeneity of the study subjects, with the majority being BPH patients, and this is not represented other potential populations such as pediatric patients underwent hypospadia repair. Third, all studies we included were retrospective, and thus may subjected to recall bias.

Conclusion

The risk factors of urethral stricture in this study includes the dose of brachyterapy for prostate cancer patients, lower resection speed of BPH, prolonged operative time, intraoperative urethral mucosa rupture, post-operative continuous infection, the diameter of the instrument, presence of chronic prostatitis in anamnesis, increased volume of the prostate, repeated drainage of the bladder using the urethral catheter, high comorbidity burden, second TURP surgery, history of preoperative catheter insertion, high postoperative WBC, and long postoperative catheterization time.

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