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Balloon dilation for the treatment of male urethral strictures: A Systematic Review and Meta-analysis

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Abstract

Objective: The minimally invasive endoluminal treatment of urethral strictures has been a topic of concern for decades. The aim of this study is to review and discuss the safety, efficacy and influencing factors of balloon dilatation for male urethral stricture.

Design: Systematic review and meta-analysis.

PROSPERO registration number: CRD42022334403.

Data sources: Embase, Medline, Web of Science, Cochrane Library and Scopus were searched for publications before July 17, 2022.

Study selection: Two independent researchers screened and assessed the results, and all clinical studies on balloon dilation for the treatment of urethral strictures in men were included.

Data extraction and synthesis: Success rate, rate of adverse events, International Prostate Symptom Scores (IPSS), maximum uroflow (Qmax) and post-void residual urine volume (PVR) were the main outcomes. Stata 14.0 was used for statistical analysis.

Results: 15 studies with 715 patients were finally included in this systematic review. Pooled results of eight studies showed that the reported success rate of simple balloon dilation for male urethral strictures was 67.07% (95% CI: 55.92%-77.36%). The maximum urinary flow rate at 3 months (RR=2.6510, 95% CI: 1.0681-4.2338, $p < 0.01$) and the maximum urinary flow rate at one year (RR=1.6637, 95% CI: 1.1837-2.1437, $p < 0.05$) were significantly changed after dilation. There is insufficient evidence to suggest that balloon dilation is superior to optical internal urethrotomy (OIU) and direct visual internal urethrotomy (DVIU) (RR=1.4754, 95%CI: 0.7306-2.9793, p=0.278).

Conclusion: Balloon dilatation may be an important intermediate choice for the treatment of male urethral stricture. The etiology, location, length, previous treatment and other comprehensive factors of urethral stricture may be associated with the efficacy of balloon dilation.

Key words: Balloon dilation, urethral stricture, systematic review, meta-analysis

Strengths and limitations of this study

As of January 14, 2023, this is the first systematic review of balloon dilation for men with urethral strictures. All clinical studies on balloon dilation for the treatment of urethral strictures in men were included.

Although the information we can obtain is quite limited, the relevant influencing factors analyzed and discussed in this study should be concerned in the future development of balloon dilation.

Balloon dilation of urethral stricture to date has no sufficient statistical power to be recommended and to become a clinically standpoint. More high-quality randomized clinical trials are needed to provide stronger evidence of the benefits of balloon dilation.

1. Introduction

As an ancient disease relatively common in men, urethral stricture refers to any abnormal narrowing of the anterior or posterior urethra. In some susceptible populations, the incidence of male urethral stricture disease is as high as 0.6%, with more than 5,000 hospitalizations per year [1]. The most typical symptoms of patients are weakened urine flow and even urinary retention, which seriously affects the quality of life [2]. The etiology of urethral stricture is complex, including trauma, infection, iatrogenic, lichen sclerosus, idiopathic, etc. Iatrogenic urethral injury is the most common cause in resource-rich countries, whereas infections and trauma are more common in developing countries [3, 4]. With the continuous development of medical technology, the rapid increase in the incidence of iatrogenic urethral stricture is an urgent problem to be solved. Catheterization, transurethral manipulation, prostate surgery, radiotherapy, and chemotherapy can all cause irreversible stricture damage to the urethra [5-8].

Although urethroplasty has been recognized as the curative treatment for urethral strictures, dilation and direct visual internal urethrotomy (DVIU) are still widely used and effective for single bulbar urethral strictures < 2 cm (especially < 1 cm) with the success rate of 35-70 % [3, 9]. There is currently a lack of evidence to evaluate whether dilation or DVIU is more effective, so both have the same therapeutic indications [10].

Balloon dilation is a special type of dilation that has a long history of treating urethral strictures in men. Russinovich, N. A. E. et al were the first to report preliminary results of 7 cases of male urethral strictures treated with balloon dilation in 1980, which was painless compared to traditional dilation methods and associated mucosal and periurethral injury [11]. Subsequently, Pinot, J. J. dilated the urethra of 25 patients using an inflatable balloon catheter, which included atraumatic catheterization through a vascular catheter under urethoscopy, followed by inflation of the balloon catheter into a flexible guide [12]. The dilation was controlled by voiding urethrography and was much less uncomfortable than conventional urethral dilation, with recurrence in only 3 of 25 patients. Immediately, Glesy, J. D. designed a new coaxial balloon dilator for the treatment of urethral stricture, and pointed out that the balloon dilator can expand slowly and gradually, which is better than the traditional rapid and sudden expansion [13]. More studies have shown that balloon dilation produces minimal trauma and immediate symptom relief, with less patient discomfort and a low complication rate [14-19]. Since angiography has a certain degree of radioactivity, B-ultrasound has been used in the control of balloon dilation, and good clinical results have been initially achieved [20]. Further research found that direct visually controlled balloon dilation under cystoscopy can gently dilate the urethra with higher safety and efficacy [21].

As is a well-tolerated minimally invasive endourology procedure widely used in the clinical management, balloon dilation may have higher accuracy and lower complication rates than simple dilation, and a longer recurrence-free time. Our

objective was to assess the efficacy and safety of balloon dilation and its associated influencing factors.

2. Materials and methods

2.1 Search strategy

This study followed the guidelines of the PRISMA statement [22], and the specific protocol was registered on PROSPERO with the registration number CRD42022334403. Performing with Medical Subject Headings and free text terms, we searched the relevant records published prior to July 17, 2022 in the following databases: Medline, Embase, Cochrane Library, Web of Science and Scopus. The major search terms were "Urethral Stricture" or "Urethral Stenosis" and "Balloon" and "Dilatation" or "Dilation" in English. Information on studies in progress was sought by searching relevant trial registers including ClinicalTrials.gov.

2.2 Eligibility criteria

Two researchers (X.L. and C.X.) screened and assessed the search results independently. The inclusion criteria included: (1) male patients diagnosed as urethral strictures; (2) balloon dilation was applied as the main intervention, not including patient self-dilation; (3) clinical studies about patients, retrospective or prospective; (4) report of the success rate and the rate of adverse events.

Conference abstracts were eligible for inclusion if they reported sufficient outcome data. If several articles were all related to the same study, the most recent publication with the most complete data was included in the systematic review. The consensus was finally reached through consultation and discussion in the event of any disagreement and differences between the two researchers.

2.3 Quality assessment

According to the type of study, the quality of included studies was independently assessed by two researchers (X.L. and C.X.). All observational studies were assessed using the Newcastle-Ottawa Scale (NOS) in terms of population selection, comparability, and outcome evaluation [23]. Randomized controlled trial (RCT) studies were assessed using the Jadad Quality Scale, and articles with the score >3 were considered as high-quality research [24]. For single-arm clinical trials, the first 8 items of the Methodological Index for Non-randomized Studies (MINORS) scale were used for assessment[25].

2.4 Data extraction

We extracted data on success rate, rate of adverse events, International Prostate Symptom Scores (IPSS), maximum uroflow (Qmax, mL/sec) and post-void residual urine volume (PVR). When disagreements arise, a third reviewer will participate in discussions and mediate to reach a consensus.

2.5 Statistics analysis

Stata 14.0 (StataCorp, USA) was applied for statistical analysis, reporting success rate and adverse effects rate as proportions. I^2 index was used to test the between-study heterogeneity. When $I^2 > 50\%$, it was considered significant heterogeneity and the random effects model was used for pooled analysis, otherwise less heterogeneity was considered and the fixed effects model was used.

2.6 Patient and public involvement

None.

3. Results

3.1 Study selection and risk of bias

The flowchart of the study retrieval process is shown in Fig 1. A total of 715 articles were identified from the initial search of the aforementioned databases, of which 335 articles were excluded as duplicates. Titles, keywords and abstracts were reviewed and 72 initial records were retained. Through the evaluation of the full text, 57 of them were excluded. For articles referring to the same clinical trial, we only reserve the latest and most comprehensive ones. Ultimately, we included 15 studies for systematic review with a total of 842 patients.

Table 1 presents the main characteristics of the included studies. These articles were published from 1988-2022, with 13 articles published after 2010 accounting for the vast majority. Of these, there are 1 randomized controlled trial [26], 2 single-arm clinical trials [27, 28], 2 case-control studies [29, 30], and 10 retrospective case studies [31-40].

There was considerable risk of bias in the meta-analyses, most of which stemmed from the retrospective design of the studies and the lack of valid controls. Since the operation is often influenced by the subjective wishes and preferences of the patients and surgeons, unavoidable selection bias may exist. Some confounding factors such as age, etiology, length of stenosis, and patient baseline physical condition were present in most studies. In addition, due to the small sample size of some of the included studies, there are certain limitations in reflecting the overall clinical situation. RCTs with better design, larger sample sizes, and more comparable control groups are needed to further illustrate the efficacy and safety of balloon dilation in the future.

Table 1: The main characteristics of included studies.

Study	Year	Country	Type of Study	Article Type	NOS Score (0-9)	Jadad Score (0-7)	MINORS Score (0-24)
Virasoro, Ramon et al.	2022	USA, Dominican Republic, Panama	Single-arm Clinical Trial	Journal article	/	/	10
Elliott, S. P. et al.	2022	USA, Canada	RCT	Journal article	/	5	/
Beeder, L. A. et al.	2022	USA	Retrospective Case Study	Journal article	3	/	/
Alibekov, M. M. et al.	2021	Russia	Retrospective Case Study	Journal article	2	/	/
Yi, Y. A. et al.	2020	USA	Retrospective Case Study	Journal article	3	/	/
Kumano, Y. et al.	2019	Japan	Case Control Study	Journal article	5	/	/
Zhou, Y. et al.	2016	China	Retrospective Case Study	Journal article	2	/	/
Yu, S. C. et al.	2016	China	Case Control Study	Journal article	6	/	/
Chhabra, J. S. et al.	2016	India	Retrospective Case Study	Journal article	3	/	/
Ishii, Gen et al.	2015	Japan	Retrospective Case Study	Journal article	3	/	/
Mao, D. et al.	2014	China	Retrospective Case Study	Journal article	2	/	/
Vyas, J. B. et al.	2013	India	Retrospective Case Study	Journal article	3	/	/
Alguersuari, A. et al.	2012	Spain	Retrospective Case Study	Conference abstract	2	/	/
MacDiarmid, S. A. et al.	2000	USA	Retrospective Case Study	Journal article	2	/	/
Mohammed, S. H. et al.	1988	Denmark	Single-arm Clinical Trial	Journal article	/	/	6

NOS, Newcastle Ottawa Scale; MINORS, Methodological Index for Non-randomized Studies.

3.2 The principle of balloon dilation

The principle of balloon expansion is to apply radial force along the balloon span at the stenosis. While the principle of traditional optical internal urethrotomy is to achieve epithelial regeneration by incising scar tissue. Compared with the parallel force brought by traditional rigid dilation, balloon dilation has less shear force and less trauma, which can reduce the risk of cavernous fibrosis and cause less discomfort [30, 41, 42]. Balloon dilation can also make the fibrous scar in the stenosis more evenly fractured, presenting a 360° annular expansion, thereby increasing the inner diameter of the stenotic segment, and during the balloon dilation process, the urethral pressure gradually increases, and the expansion is slow and gentle, so as to avoid blood vessels due to violence [13]. Squeeze bleeding has the advantage of one-time expansion. In addition, the smooth balloon can avoid normal urethral mucosal damage.

3.3 Safety assessment and incidence of adverse events

Urinary tract infection, urinary retention and postoperative hematuria and dysuria are the main complications of balloon dilation. Therefore, strict aseptic and standardized operations are required during the surgical operation to prevent and avoid the occurrence of adverse events as much as possible.

We performed a pooled analysis of reported adverse event rates for urinary tract infection and urinary retention. The pooled incidence of infection in patients after balloon dilation was 3.27% (95% CI: 1.2%-8.86%; heterogeneity: I^2=46.2589%, p= 0.1338) (Fig 2A). While, the pooled incidence of urinary retention was 8.31% (95% CI: 1.84%-18.39%; heterogeneity: I^2=84.6223%, p<0.05) (Fig 2B). Urinary tract infection is the most common complication within 30 days of balloon dilation, and some patients require antibiotic treatment [31]. Some patients also have transient hematuria after surgery, but no further treatment such as blood transfusion is required [30, 31]. Furthermore, Yu, S. C.'s study also found that the incidence of major postoperative complications such as urethral bleeding and urinary tract infection in the balloon dilatation group was lower than that in the DVIU group (urethral bleeding: 2/31 vs. 8/25, P=0.017; UTI: 1/31 vs. 6/25 P=0.037) [30].

3.4 Clinical efficacy of balloon dilation for male urethral strictures

We summarized the clinical characteristics and the efficacy of balloon dilation included in the literature, and the relevant contents are shown in Table 2 & Table 3. At present, there is a lack of objective and recognized indicators to evaluate the clinical effect of balloon dilation. Perceptions of dilation success vary among surgeons, and patients' performance on stricture recurrence is highly individual, with rates of dilation success varying across specific studies. For studies with conventional balloon dilatation, we defined success of balloon dilatation as no recurrence or no further stricture treatment during follow-up, excluding studies with a sample size of

less than 30 and merging data from 8 studies published in 2012-2022 [30, 31, 33-35, 37-39]. The pooled balloon dilatation success rate was 67.07% (95% CI: 55.92%-77.36%; heterogeneity: I^2=86.8683%, p<0.05) (Fig 3A). This result needs to be taken with caution and most likely overestimates the efficacy of balloon dilatation. Moreover, two studies on drug coated balloon in recurrent urethral stricture expressed its considerable effect on recurrent urethral stricture with relatively objective functional success rate (67%) and anatomical success rate (74.6%) [26, 27].

In addition, the changes in urinary flow rate, PVR, and IPSS scores of patients are summarized in Table 4. Compared with the preoperative condition, we found that the postoperative maximum urinary flow rate was greatly improved at 3 months (RR=2.6510, 95% CI: 1.0681-4.2338; z=3.282, p < 0.01; I^2=96.5%, p < 0.05), and the significant difference remained at one year postoperatively (RR=1.6637, 95% CI: 1.1837-2.1437; z=6.794, p < 0.01; I^2=78.8%, p < 0.05). The patient's IPSS score and PVR also decreased accordingly. With the extension of follow-up time, the quality of life of the patients remained at a good level, reflecting the long-term effectiveness of balloon dilation.

Table 2: The clinical characteristics and efficiency of balloon dilatation (Ⅰ).

Study	Evaluable Patients (n)	Age (average)	Etiology	Location of the Strictures	Length of Stenosis	Pre-dilated state
Virasoro, Ramon et al.	43	50.7 (22.0 - 81.0)	/	Anterior urethra	≤ 2 cm	1–4 prior endoscopic treatments (none within 3 months of enrollment)
Elliott, S. P. et al.	60 (79): 15 (48)*	60.6 ± 16.0 : 58.7 ± 15.5	Iatrogenic (21/78, 26.9%); Idiopathic (42/78, 53.8%); Inflammatory (1/78, 1.3%); Traumatic (14/78, 17.9%); pelvic radiation (9/79, 11.4%)	Anterior urethra	≤ 3 cm	≥ 2 prior endoscopic treatments
Beeder, L. A. et al.	91	61	/	Anterior urethra (n=75, 82%); posterior urethra (n=16, 18%)	/	Most (75/91, 82%) had prior treatment for USD (endoscopic 50/91 (55%), 51/91 (56%) urethroplasty)
Alibekov, M. M. et al.	7	52 (47 - 65)	Idiopathic (4/7, 57.1%); Inflammatory (1/7, 14.3%); Traumatic (2/7, 28.6%)	Anterior urethra	≤ 1 cm	All patients had 1 urethral stone. The sizes of the stone ranged from 4 to 9 mm (median - 6 mm)
Yi, Y. A. et al.	80	/	/	Anterior urethra (n=59, 74%); posterior urethra (n=21, 26%)	≤ 1.5 cm	Over 75% of patients had some form of prior stricture treatment, including dilation (34/80, 42.5%), DVIU (19/80, 23.8%), or urethroplasty (48/80, 60%)

Kumano, Y. et al.	13 : 9	71 : 63	Iatrogenic (10/13, 76.9%); Idiopathic (3/13, 23.1%)	Anterior urethra (n=9, 41%); posterior urethra (n=13, 59%)	/	/
Zhou, Y. et al.	45	46.6 (22 - 76)	Iatrogenic (19/45, 42.2%); Inflammatory (5/45, 11.1%); Traumatic (18/45, 40%); pelvic radiation (3/45, 6.7%)	Anterior urethra (n=36, 80%); posterior urethra (n=9, 20%)	≤ 2 cm	5 patients had a prior suprapubic cystostomy
Yu, S. C. et al.	31 : 25	49 (32 - 67) : 44 (24 - 71)	Iatrogenic (7/31, 22.6%); Idiopathic (1/31, 3.2%); Inflammatory (2/31, 6.5%); Traumatic (21/31, 67.7%);	Anterior urethra (n=45, 80%); posterior urethra (n=11, 20%)	≤ 1 cm (n=48, 86%) ; > 1 cm (n=8, 14%)	None received prior endovascular therapy
Chhabra, J. S. et al.	134 (144)*	52 (18 - 85)	Iatrogenic (59/144, 41.0%); Idiopathic (84/144, 58.3%); pelvic radiation (1/144, 0.7%)	Anterior urethra (n=110, 76%); posterior urethra (n=8, 6%); both (n=26, 18%)	≤ 1.5 cm (n=130, 90%) ; > 1 cm (n=14, 10%)	/
Ishii, Gen et al.	10	70 (61 - 75)	Iatrogenic	Posterior urethra	/	All patients had cystourethral anastomotic stricture after radical prostatectomy
Mao, D. et al.	37 (39)*	55 (24 - 84)	/	Anterior urethra (n=17, 44%); posterior urethra (n=20, 51%); both (n=2, 5%)	≤ 2 cm	/
Vyas, J. B. et al.	120	49.86 (30 - 85)	/	Anterior urethra (n=114, 95%); posterior urethra (n=6, 5%)	≤ 1.5 cm	/
Alguersuari, A. et al.	65	63.17 ± 16.9	/	Anterior urethra (26.2%); posterior urethra (73.8%)	≤ 2 cm (86.2%) ; > 2 cm (13.8%)	/
MacDiarmid, S. A. et al.	51	/	Iatrogenic (27/51, 52.9%); Idiopathic (11/51, 21.6%); Inflammatory (10/51, 19.6%); Traumatic (3/51, 5.9%)	Anterior urethra (n=49, 96%); posterior urethra (n=2, 4%)	/	/
Mohammed, S. H. et al.	6 (7)*	35 (16 - 67)	Iatrogenic (1/6, 16.7%); Idiopathic (2/6, 33.3%); Inflammatory (2/6, 33.3%); Traumatic (1/6, 16.7%)	Anterior urethra (n=4, 57%); posterior urethra (n=3, 43%)	/	/

* In parentheses are the number of people who were initially assessed at baseline in the study, and outside brackets were the number of people who could be effectively assessed at the end of the follow-up.

Table 3: The clinical characteristics and efficiency of balloon dilatation (Ⅱ).

Study	Balloon Types	Control	Definition of Success Rate	Reported Success Rate (%)	Follow-up
Virasoro, Ramon et al.	Optilume® drug coated balloon (DCB)	/	Functional success was defined as ≥50% reduction in International Prostate Symptom Score (IPSS) without need for retreatment.	67	3 years
Elliott, S. P. et al.	Optilume® drug coated balloon (DCB)	dilation / DVIU	Anatomical success: the proportion of participants in whom the surgeons could atraumatically pass a 16-French flexible cystoscope or a 14-French catheter through the treated area at 6 months	74.6 : 26.8	1 year
Beeder, L. A. et al.	8-cm, 24-French UroMax Ultra™ balloon dilator	/	Proportion of patients who reported no recurrence of lower urinary tract symptoms or did not need further stricture treatment	50	12 months (3 - 40)
Alibekov, M. M. et al.	/	/	Proportion of patients without recurrence of urethral stricture after 18 months of dilation	85.7	14 months (3 - 24)
Yi, Y. A. et al.	8-cm, 24-French UroMax Ultra™ balloon dilator	/	Proportion of patients with postoperative urethral stricture who did not recur or did not need further stricture treatment	66.3	8.4 months (IQR, 3.9 - 22.5)
Kumano, Y. et al.	Balloon dilation catheter (X-FORCE; BARD Medical, Murray Hill, NJ, USA)	OIU	Proportion of patients with no recurrence of stenosis during the follow-up period	84 : 22	/
Zhou, Y. et al.	Balloon catheter (X-Force™, C.R. Bard Inc., USA)	/	Proportion of patients without further stricture treatment during the follow-up period	86.7	6 - 24 months
Yu, S. C. et al.	6-cm, 7-French balloon catheter (X-Force™, C.R. Bard Inc., USA)	DVIU	Proportion of patients with postoperative urethral stricture who did not recur or did not need further stricture treatment	35.5	14.75 months (5 - 36)
Chhabra, J. S. et al.	8-cm, 24-French urethral Balloon catheter set (Cook Urological, Spencer, Ind., USA)	/	Proportion of patients without further stricture treatment during the follow-up period	84.4	24 months (3 - 52)
Ishii, Gen et al.	6-cm, 6-French Balloon catheter, the X Force®	/	Proportion of patients with no recurrence of stenosis during the follow-up period	80	24 months (7 - 67)
Mao, D. et al.	24-French Nephrostomy balloon dilation catheter, the X Force®	/	Proportion of patients without further stricture treatment during the follow-up period	64.9	/

Vyas, J. B. et al.	8-cm, 24-French urethral Balloon catheter set (Cook Urological, Spencer, Ind., USA)	/	Proportion of patients without further stricture treatment during the follow-up period	68	6 months (2 - 60)
Alguersuari, A. et al.	fluoroscopic- guided balloon dilation	/	Proportion of patients without further stricture treatment during the follow-up period	69	/
MacDiarmid, S. A. et al.	The UrethraMax (4, 6, or 8-cm; 24-French) or a coude tip balloon dilation catheter	/	Proportion of patients without further stricture treatment during the follow-up period	55	9 months (1 - 16)
Mohammed, S. H. et al.	Olbert balloon catheter	/	Proportion of patients without further stricture treatment during the follow-up period	66.7	12 months (6 - 26)

DVIU, direct vision internal urethrotomy; OIU, optical internal urethrotomy.

Table 4: Changes in urinary flow rate, PVR, and IPSS scores of patients after balloon dilation. (The following table is continued to the right)

Study	Location of the Strictures	Length of Stenosis
Virasoro, Ramon et al. 2022	Anterior urethra	≤ 2 cm
Elliott, S. P. et al. 2022	Anterior urethra	≤ 3 cm
Zhou, Y. et al. 2016	Anterior urethra (n=36, 80%); posterior urethra (n=9, 20%)	≤ 2 cm
Chhabra, J. S. et al. 2016	Anterior urethra (n=110, 76%); posterior urethra (n=8, 6%); both (n=26, 18%)	≤ 1.5 cm (n=130, 90%) ; > 1 cm (n=14, 10%)
Vyas, J. B. et al. 2013	Anterior urethra (n=114, 95%); posterior urethra (n=6, 5%)	≤ 1.5 cm
MacDiarmid, S. A. et al. 2000	Anterior urethra (n=49, 96%); posterior urethra (n=2, 4%)	/

IPSS					
Before surgery	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
25.2 ± 4.5 （n=53)	6.1 ± 7.6 (n=51)	4.6 ± 5.2 (n=45)	4.5 ± 3.9 (n=40)	6.9 ± 7.7 (n=38)	5.5 ± 6.9 (n=33)
22.0 ± 6.8 （n=79)	7.4 ± 5.8 (n=74)	8.3 ± 6.2 (n=71)	9.0 ± 7.1 (n=67)	/	/
/	/	/	/	/	/

/	/	12.7 (n=112)	12.6 (n=112)	/	/
21.6 (n=120)	11.4 (n=120)	12.6 (n=120)	/	/	/
/	/	/	/	/	/

Qmax (mL/sec)					
Before surgery	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
5.0 ± 2.6 (n=46)	22.2 ± 12.5 (n=51)	19.8 ± 10.8 (n=45)	20.1 ± 10.0 (n=39)	17.5 ± 10.4 (n=38)	15.1 ± 8.3 (n=33)
7.6 ± 3.4 (n=78)	18.6 ± 10.9 (n=71)	16.6 ± 8.9 (n=69)	15.5 ± 9.0 (n=65)	/	/
5.6 ± 1.4 (n=45)	19.8 ± 3.9 (n=45)	/	/	/	/
5.2 ± 2.7 (n=144)	/	15.4 ± 7.2 (n=112)	12.6 ± 5.7 (n=112)	/	/
5.7 (n=120)	14.3 (n=120)	12.7 (n=120)	/	/	/
10.4 (n=48)	15.3 (n=43)	17.7 (n=27)	15.2 (n=5)	/	/

PVR (mL)					
Before surgery	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
141.4 ± 105.1 (n=43)	141.4 ± 105.1 (n=51)	30.0 ± 42.8 (n=45)	24.6 ± 32.1 (n=39)	45.5 ± 49.5 (n=38)	50.2 ± 62.5 (n=33)
109.8 ± 116.9 (n=77)	103.4 ± 134.4 (n=70)	73.1 ± 117.7 (n=67)	94.6 ± 121.8 (n=66)	/	/
/	/	/	/	/	/
/	/	/	/	/	/
90.2 (n=120)	34.2 (n=120)	20.2 (n=120)	/	/	/
/	/	/	/	/	/

IPSS, International Prostate Symptom Scores; Qmax, maximum uroflow; PVR, post-void residual urine volume.

3.5 Comparison of balloon dilation with other endoluminal treatments

We conducted a separate analysis of two studies compared with DVIU and optical internal urethrotomy (OIU), finding no statistically significant difference in efficacy between conventional balloon dilation and other traditional endoluminal therapy (RR=1.4754, 95%CI: 0.7306-2.9793; z=1.085, p=0.278; heterogeneity: I^2=0%, p=0.351) (Fig 3B). There is insufficient evidence to suggest that balloon dilation is superior to other traditional endoluminal therapies.

3.6 Clinical preference and efficacy influencing factors of balloon dilation

3.6.1 Etiology

We pooled eight studies of simple balloon dilation that addressed specific etiologies [28-30, 32, 34-36, 40], involving a total of 307 patients. Iatrogenic urethral strictures (43.32%, 133/307) and idiopathic urethral strictures (34.20%, 105/307) accounted for the vast majority. The stenosis caused by trauma and inflammation accounted for 14.66% (45/307) and 6.51% (20/307) respectively. There were also 4 patients suffering from radiation. Although this is only a one-sided epitome, it follows the trend that iatrogenic injury may become the main etiology of urethral stricture in males in the future. The persistence of idiopathic factors such as lichenoid sclerosis is a serious challenge that has to be overcome.

Due to the lack of meticulous subgroup analysis in the included literatures, it is difficult for us to directly compare the efficacy difference among strictures caused by different etiologies. The influence of etiology on the efficacy of balloon dilatation depends primarily on the type of stenotic pathology it creates and the specific stenotic segment length and location. The essence of balloon dilation is the expansion of physical properties, which needs to avoid the re fibrosis of scar tissue in the narrow segment to the greatest extent. Once the process of re-fibrosis progresses, strictures are highly likely to recur. Therefore, balloon dilation may not perform well for stenosis with high degree of fibrosis. Lichen sclerosus is the most prominent cause of idiopathic urethral strictures. The narrow segment pathologic features of lichen sclerosus include hyperkeratosis or epithelial atrophy, basal cell vacuolar degeneration, lichenoid lymphocytic infiltration, and upper epithelial sclerosis [43]. This epithelial stromal lesion lesion lesion characterized by squamous atrophy or hyperplasia is distinct from the fibrotic pathologic characterization of most urethral strictures. A recent review pooling expert opinion in urology stated dilatation is unlikely to be a successful long-term solution for lichenoid sclerosing urethral stricture, potentially triggering longer adverse outcomes [44]. Balloon dilatation of physical nature is difficult to fundamentally improve the condition of patients with idiopathic urethral strictures pathogenetically, and its clinical indications require strict control.

3.6.2 Location of urethral stricture

We combined 11 studies that identified the location of stenosis [28, 31-40]. The patients with anterior urethral stricture accounted for 74.28% (488/657), the patients with posterior urethral stricture accounted for 21.77% (143/657), and 3.95% (26/657) patients had both strictures. The majority of patients receiving balloon dilatation are patients with anterior urethral stricture, since its high incidence rate.

Moreover, we combined data from two studies that performed subgroup analysis of stricture location [31, 33] and did not find any statistical difference in the efficacy of balloon dilatation between anterior and posterior urethral strictures (RR=0.9568, 95%CI: 0.6618-1.3832, p=0.814) (Fig 4A).

3.6.3 Length of urethral stricture

We performed a subgroup analysis of eight simple balloon dilatation studies that were involved in the combination of success rates previously [30, 31, 33-35, 37-39], and the results were shown in Fig 4B. In shorter stenoses (≤ 2cm), the success rate of balloon dilation was up to 71.58% (95% CI: 61.93%-80.35%), and heterogeneity was also reduced (I^2=63.2342%, $p < 0.05$) (Fig 4B). In a study of patients with anterior urethral strictures of less than 1 cm in length, the success rate was as high as 85.7% [32]. The reduction in heterogeneity of the pooled results suggests that the stenotic segment length is a prognostic factor, and balloon dilatation may have a higher success rate in short segment urethral strictures.

3.6.4 Age

We further stratified the previous eight studies [30, 31, 33-35, 37-39] on account of different age groups, the results were shown in Fig 4C. In the age group of 50 to 60 years, the success rate of balloon dilation was 80.79% (95% CI: 74.42%-86.47%). However, when the patients were over 60 years old, the success rate dropped to 58.49% (95% CI: 50.61%-66.17%). Interestingly, the combined success rate was at 65.39% (95% CI: 39.61%-87.22%) in relatively young patients, probably because part of the reported younger patient had a more severe stenosis. The etiology of strictures in elderly patients is often iatrogenic, whereas in younger patients more complex urethral strictures can be caused by relatively specific factors such as trauma and lichenoid sclerosis gonorrhea. Even though the success rate is somewhat subjective, we can roughly see the decreasing trend of the efficacy of balloon dilation in elderly patients.

3.6.5 Prior intervention management

A separate analysis of patients who had received prior endoscopic management (catheter/balloon dilation, direct visual internal urethrotomy) in two studies [31, 33] was performed and we found that balloon dilation had a pooled success rate of 49.51% (95% CI: 39.79%-59.26%) (Fig 4D). In patients with previous surgical intervention, the efficacy of balloon dilation may be diminished. Based on the limited data available in these two studies [31, 33], we compared patients with and without previous urethroplasty, and found no statistical difference in the success rate of simple balloon dilatation (RR=1.1682, 95%CI: 0.6160-2.2153, p=0.634) (Fig 5A). The

prevailing clinical view is that repeated endoluminal intervention may render further endoluminal treatment less effective, but this needs to be confirmed by clinical studies with larger sample sizes.

3.6.6 Other patient status

We performed a more nuanced subgroup analysis of the two studies [31, 33] that provided some patient baseline details. There was no statistically significant difference in balloon dilation efficacy between patients with a history of smoking and non-smoking patients (RR=1.1052, 95%CI: 0.8083-1.5112, p=0.531) (Fig 5B). Chronic diseases such as coronary artery disease (RR=1.0714, 95%CI: 0.7618-1.5069, p=0.692), diabetes mellitus (RR=0.9144, 95%CI: 0.6118-1.3666, p=0.662), hypertension (RR=0.8377, 95%CI: 0.6121-1.1464, p=0.269), and chronic obstructive pulmonary disease (RR=1.3515, 95%CI: 0.7495-2.4374, p=0.317) also did not show statistical differences in the efficacy of balloon dilation (Fig 5C-F). Our preliminary analysis results suggest that patient status such as poor living habits and chronic diseases may not have a significant impact on the efficacy of balloon dilation.

3.7 Intermittent urethral balloon self-dilation

Patient self-balloon dilation is a specific form of balloon dilation, and we also briefly review its clinical evaluation. Urethral dilation is easy to perform and can be performed by the patient at home, avoiding repeated hospitalizations and frequent general anesthesia [45]. A study by Levine, L. A. [46] suggests that adjuvant home balloon self-dilation may be a potential option for patients at high risk of recurrence. In this study of 25 evaluable patients, the majority of patients noted that balloon dilation improved voiding and maintained or improved peak urinary flow rate at an average of 18.7 months of long-term follow-up. Nonetheless, six patients (19%) complained of balloon placement discomfort, 3 (10%) noted minor bleeding during dilation, and 4 (13%) developed urinary tract infections during follow-up. Hennessey, D. B.'s initial experience with self-expanding balloon dilation in the outpatient setting was encouraging, with all 11 patients reporting that they were very satisfied or satisfied with overall outcomes and quality of life [47]. A recent study reported in 2021 stated that the self-urethral balloon dilatation offers patients with complex strictures, especially those with a history of radiation, an opportunity to avoid surgical intervention [48].

However, due to the imprecision of patient self-balloon dilation, which may cause complications and even aggravate injury. As early as the last century, scholars have shown that short-term postoperative self-dilation techniques do not appear to prevent recurrence of strictures in patients treated with endourethral incisions [49]. A recent meta-analysis of patient self-dilation also indicated that the quality of evidence for this approach to reduce the risk of recurrent urethral strictures is very low [50]. Although self-dilation is very convenient and avoids the complications of surgery, it is not suitable for all patients, and not all patients can master the skills and techniques of dilation. Self-balloon dilation by the patient needs to be further weighed against surgery, and well-designed randomized controlled trials are needed to determine

whether this benefit of convenience is sufficient to make this intervention worthwhile.

4. Discussion

With the gradual increase of iatrogenic urethral strictures, the surgeon should choose the appropriate treatment method according to the etiology of the urethral stricture, the location and length of the stricture, and the degree of urethral fibrosis.

Even though there is no clear evidence that the clinical efficacy of balloon dilation is significantly better than that of other endoluminal treatments, balloon dilation still has a large clinical plasticity. The study by Yu, S. C. et al found that the balloon dilation operation time was much shorter than DVIU (13.19±2.68) min vs (18.44±3.29) min, P<0.01) [30], highlighting the operational simplicity of balloon dilation. The main disadvantage of internal urethrotomy is the inability to accurately estimate the depth of scar tissue during the procedure, resulting in imprecise scar tissue incisions. There may also be damage to the corpus cavernosum below the urethra, and vascular disruption in the corpus cavernosum and localized extravasation of urine through mucosal fissures may exacerbate corpus cavernosum fibrosis, eventually leading to recurrence of strictures [30, 51]. Some scholars believe that balloon dilation tends to be performed in less fibrotic cases without urethral cavernous fibrosis, speculating that the role of balloon dilation will not invade the deep urethral membrane, therefore, even if the dilation time is longer, the restenosis rate of balloon dilation is lower than optical internal urethrotomy [29]. The study by Yu, S. C. et al found the same overall stenosis-free survival with balloon dilation compared with DVIU, but most recurrent disease occurred 12 months after initial balloon dilation treatment [30]. In Kumano, Y.'s study, the balloon dilatation group had significantly longer stenosis-free times than optical internal urethrotomy (p<0.01), with median (mean) stenosis-free times of 1675 (1673) and 244 (599) days, respectively [29].

The advent and use of drug-coated balloons can reduce inflammation and reduce relapse rates by releasing drugs such as immunosuppressants while expanding. Barbalias, D. et al conducted animal experiments using paclitaxel-coated balloons and found that paclitaxel could break through the urothelial barrier and immediately distribute to the urothelium, submucosa and smooth muscle layers of the normal rabbit urethra after dilation [52]. The drug can penetrate the epithelium and act on the deep urethral tissue, effectively reduce inflammation and inhibit urethral fibrosis. In the recent ROBUST I trial [27], Optilume drug coated balloon (DCB) maintained symptomatic improvement for 3 years after treatment in a highly susceptible population with recurrent urethral strictures. The 43 patients in this trial had a functional success rate of 67%, a retreatment-free rate of 77%, and an improvement in mean IPSS from 25.2 at baseline to 5.5 at 3 years (p<0.0001). One-year results from another RCT (ROBUST Ⅲ trial) [26] showed that Optilume DCB had a significantly higher dissection success rate at 6 months than the DVIU group (75% vs 27%, p<0.001). Immediate symptoms and urinary flow rates were significantly improved in both groups, but the effects were significantly more durable in the Optilume DCB group. The United States Food and Drug Administration (FDA) has approved the

Optilume Device for the treatment of male urethral strictures [53]. Nevertheless, in the ROBUST III study [26], the incidence of serious adverse events in the control group (DVIU / simple dilation) and DCB group was 16.7% and 10.1%, respectively. The types and incidence of adverse events in the two groups were very matched, but the incidence of postoperative hematuria and dysuria was higher in the DCB group than in the control group (11.4% and 2.1% for both event types, respectively). Besides, beta-irradiation therapy with use of the rhenium-188 mercaptoacetyltriglycine-filled balloon is expected to prevent or delay stenosis recurrence in patients with recurrent urethral strictures, and the mean treatment interval increased from 2.2 months before balloon dilation to 10.7 months after treatment [54]. The design of new balloons such as cutting balloons and the exploration of some new expansion techniques may be another important direction in the future [55, 56]. The new type of balloon should meet the biomechanical requirements to better fit the narrow urethra.

On account of the lack of scientific research design, the current literature attempts to obtain good outcome evaluation data with meticulous follow-up. The use of endoscopic urethroplasty combined with balloon dilation for traumatic destruction of the prostatic membranous urethra has been previously reported [58]. Balloon dilation may provide an intermediate step before repeat dilation, urethrostomy, or urethroplasty, making it a promising alternative to current endoscopic treatment. The timing of balloon dilation is critical, and the corresponding sequential therapy combination is also worthy of further discussion. In addition, population aging and regional economic development are also factors that affect medical conditions. Compared with repeated dilation and urethrotomy, balloon dilation has a lower cost and can improve the efficiency of clinical turnover, and is expected to be further promoted in developing countries [57, 58].

Contribution Statement

Study concept and design: X.L, C.X
Acquisition of data: X.L, X.J, C.X
Analysis and interpretation of data: X.L, X.J, C.X
Drafting of the manuscript: X.L, C.X
Critical revision of the manuscript for important intellectual content: X.L, C.X, Z.Z, T.C, Z.G, J.L
Statistical analysis: X.L, X.J
Study supervision: J.L

Acknowledgement

None.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Statement of Ethics

The outcome of this meta-analysis could improve clinical decision and help to reduce the risk and cost of patients. All patients included in this study have signed informed consent during the course of each trial. And specific methods of assessment in each trial have been illustrated above. This systematic review did not any addition intervention to all included individuals. Thanks to all the patients and researchers included for their contribution to this study.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Fig 1: Flow diagram of study selection.

Fig 2: Forest plots showing the safety of balloon dilation. (A) Incidence of infection; (B) Incidence of urinary retention. CI, confidence interval.

Fig 3: Forest plots showing the efficacy of balloon dilation. (A) Success rate of simple balloon dilation; (B) Balloon dilation (Drug-coated balloons excluded) compared with simple dilation, DVIU, and optical internal urethrotomy (OIU). CI, confidence interval.

Fig 4: Forest plots showing the possible influencing factors of balloon dilation (Ⅰ). (A) Location of urethral stricture; (B) Length of urethral stricture; (C) Age; (D) Prior endoscopic management. CI, confidence interval.

Fig 5: Forest plots showing the possible influencing factors of balloon dilation (Ⅱ). (A) with and without previous urethroplasty; (B) History of smoking; (C) Coronary heart disease; (D) Diabetes mellitus; (E) Hypertension; (F) Chronic obstructive pulmonary disease. CI, confidence interval.

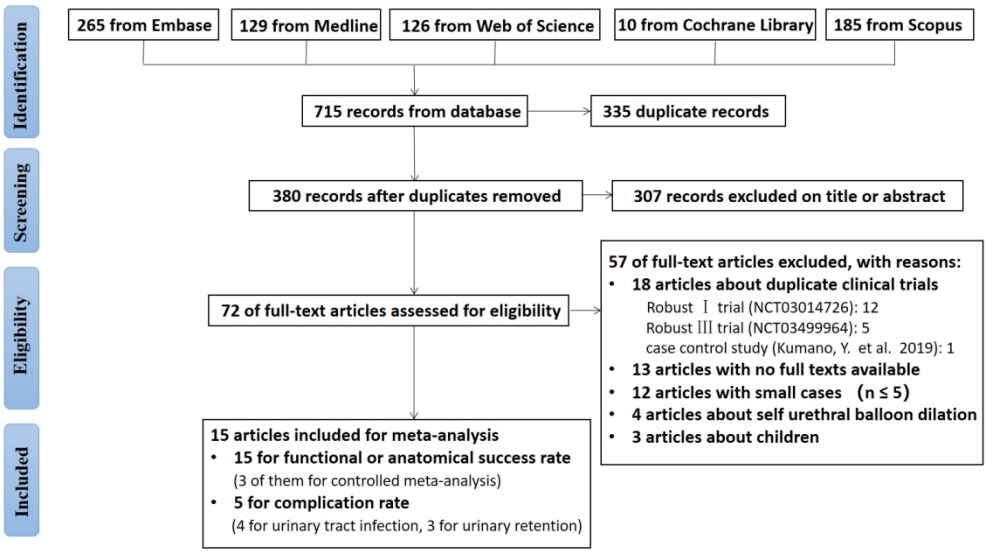

Fig 1: Flow diagram of study selection.

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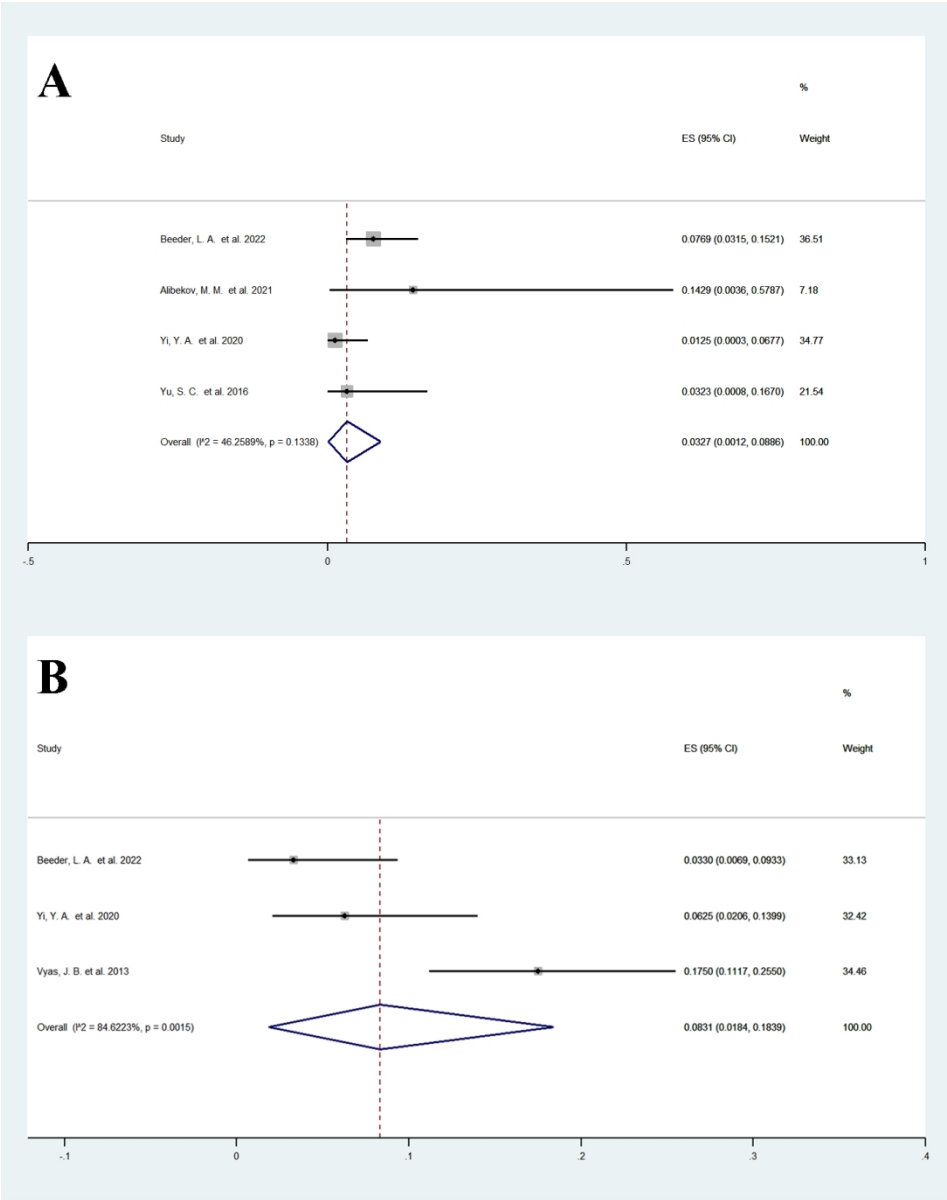

Fig 2: Forest plots showing the safety of balloon dilation. (A) Incidence of infection; (B) Incidence of urinary retention. CI, confidence interval.

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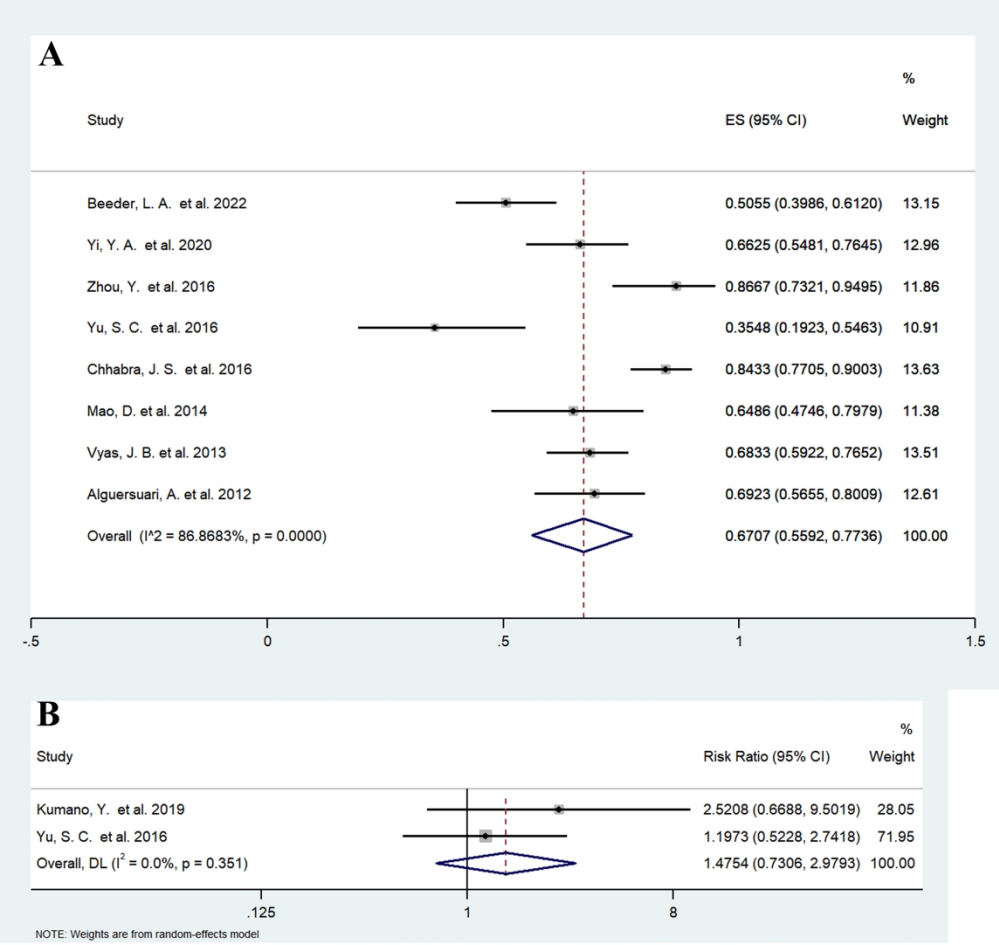

Fig 3: Forest plots showing the efficacy of balloon dilation. (A) Success rate of simple balloon dilation; (B) Balloon dilation (Drug-coated balloons excluded) compared with simple dilation, DVIU, and optical internal urethrotomy (OIU). CI, confidence interval.

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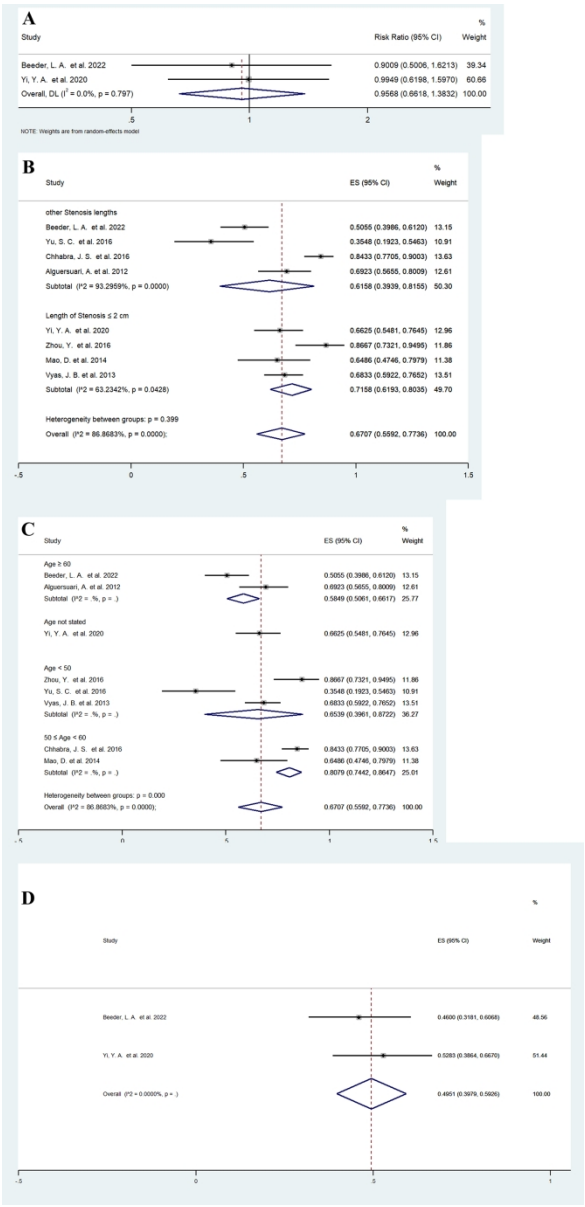

Fig 4: Forest plots showing the possible influencing factors of balloon dilation (I). (A) Location of urethral stricture; (B) Length of urethral stricture; (C) Age; (D) Prior endoscopic management. CI, confidence interval.

144x297mm (300 x 300 DPI)

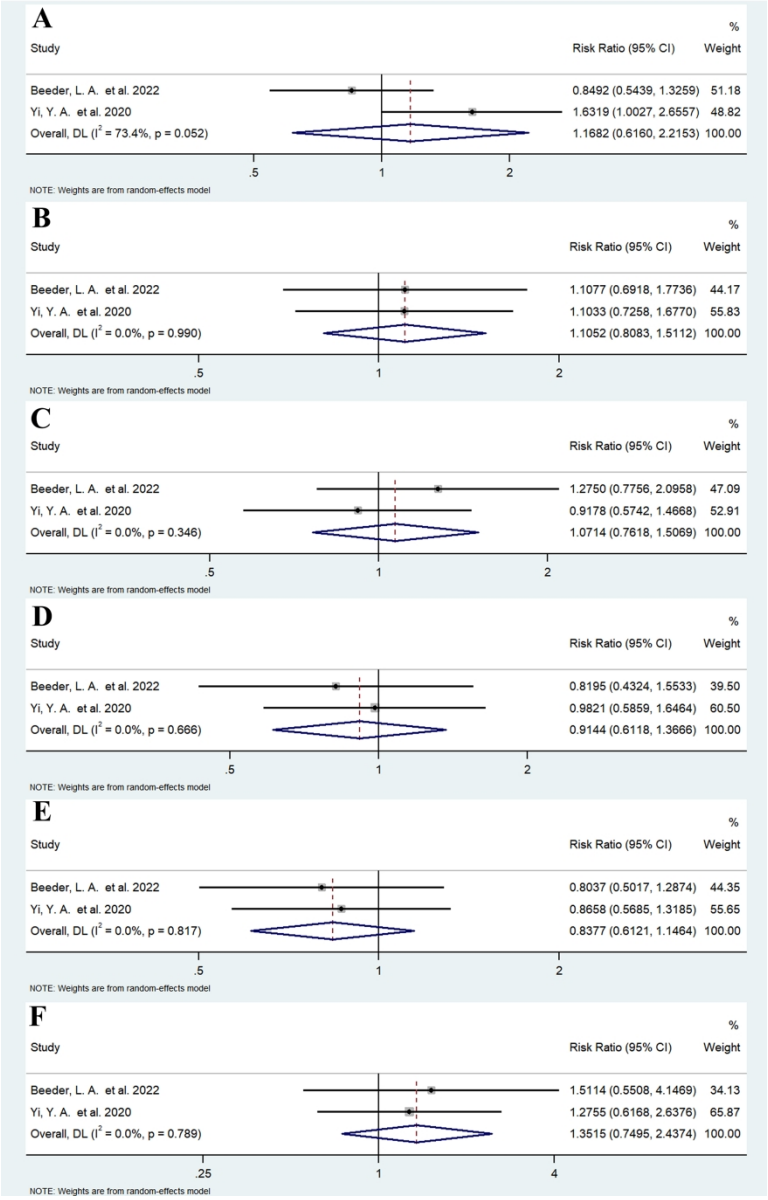

Fig 5: Forest plots showing the possible influencing factors of balloon dilation (Ⅱ). (A) with and without previous urethroplasty; (B) History of smoking; (C) Coronary heart disease; (D) Diabetes mellitus; (E) Hypertension; (F) Chronic obstructive pulmonary disease. CI, confidence interval.

189x297mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4, 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4, 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4, 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4, 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4, 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6, 7, 8, 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6, 7, 8, 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6, 7, 8, 9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6, 7, 8, 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6, 7, 8, 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6, 7, 8, 9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	10
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	10, 11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2, 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2, 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	12

PRISMA 2020 Checklist

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Balloon dilation for the treatment of male urethral strictures: A Systematic Review and Meta-analysis

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Balloon dilation for the treatment of male urethral strictures: A Systematic Review and Meta-analysis

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Abstract

Objective: The minimally invasive endoluminal treatment of urethral strictures has been a topic of concern for decades. The aim of this study is to review and discuss the safety, efficacy and influencing factors of balloon dilation for male urethral stricture.
Design: Systematic review and meta-analysis.
PROSPERO registration number: CRD42022334403.
Data sources: Embase, Medline, Web of Science, Cochrane Library and Scopus were searched for publications before July 17, 2022.
Study selection: Two independent researchers screened and assessed the results, and all clinical studies on balloon dilation for the treatment of urethral strictures in men were included.
Data extraction and synthesis: Success rate, rate of adverse events, International Prostate Symptom Scores (IPSS), maximum uroflow (Qmax) and post-void residual urine volume (PVR) were the main outcomes. Stata 14.0 was used for statistical analysis.
Results: 15 studies with 715 patients were finally included in this systematic review. Pooled results of eight studies showed that the reported success rate of simple balloon dilation for male urethral strictures was 67.07% (95% CI: 55.92%-77.36%). The maximum urinary flow rate at 3 months (RR=2.6510, 95% CI: 1.0681-4.2338, $p < 0.01$) and the maximum urinary flow rate at one year (RR=1.6637, 95% CI: 1.1837-2.1437, $p < 0.05$) were significantly changed after dilation. There is insufficient evidence to suggest that balloon dilation is superior to optical internal urethrotomy (OIU) and direct visual internal urethrotomy (DVIU) (RR=1.4754, 95%CI: 0.7306-2.9793, p=0.278).
Conclusion: Balloon dilatation may be an important intermediate choice for the treatment of male urethral stricture. The etiology, location, length, previous treatment and other comprehensive factors of urethral stricture may be associated with the efficacy of balloon dilation.

Key words: Balloon dilation, urethral stricture, systematic review, meta-analysis

Strengths and limitations of this study

- This study systematically reviewed the principle, safety, and efficacy of balloon dilatation, and also describes intermittent urethral balloon self-dilation.
- We provide a comprehensive analysis of factors such as etiology, stricture location, stricture length, and prior intervention management, and discuss clinical directions for balloon dilation.
- The quality of the included studies was relatively low and there is a considerable risk of bias.
- Most of the included studies are retrospective observational studies that lack valid controls, and the results need to be treated with caution.

1. Introduction

As an ancient disease relatively common in men, urethral stricture refers to any abnormal narrowing of the anterior or posterior urethra. In some susceptible populations, the incidence of male urethral stricture disease is as high as 0.6%, with more than 5,000 hospitalizations per year [1]. The most typical symptoms of patients are weakened urine flow and even urinary retention, which seriously affects the quality of life [2]. The etiology of urethral stricture is complex, including trauma, infection, iatrogenic, lichen sclerosus, idiopathic, etc. Iatrogenic urethral injury is the most common cause in resource-rich countries, whereas infections and trauma are more common in developing countries [3, 4]. With the continuous development of medical technology, the rapid increase in the incidence of iatrogenic urethral stricture is an urgent problem to be solved. Catheterization, transurethral manipulation, prostate surgery, radiotherapy, and chemotherapy can all cause irreversible stricture damage to the urethra [5-8].

Although urethroplasty has been recognized as the curative treatment for urethral strictures, dilation and direct visual internal urethrotomy (DVIU) are still widely used and effective for single bulbar urethral strictures < 2 cm (especially < 1 cm) with the success rate of 35-70 % [3, 9]. There is currently a lack of evidence to evaluate whether dilation or DVIU is more effective, so both have the same therapeutic indications [10].

Balloon dilation is a special type of dilation that has a long history of treating urethral strictures in men. Russinovich, N. A. E. et al were the first to report preliminary results of 7 cases of male urethral strictures treated with balloon dilation in 1980, which was painless compared to traditional dilation methods and associated mucosal and periurethral injury [11]. Subsequently, Pinot, J. J. dilated the urethra of 25 patients using an inflatable balloon catheter, which included atraumatic catheterization through a vascular catheter under urethoscopy, followed by inflation of the balloon catheter into a flexible guide [12]. The dilation was controlled by voiding urethrography and was much less uncomfortable than conventional urethral dilation, with recurrence in only 3 of 25 patients. Immediately, Glesy, J. D. designed a new coaxial balloon dilator for the treatment of urethral stricture, and pointed out that the balloon dilator can expand slowly and gradually, which is better than the traditional rapid and sudden expansion [13]. More studies have shown that balloon dilation produces minimal trauma and immediate symptom relief, with less patient discomfort and a low complication rate [14-19]. Since angiography has a certain degree of radioactivity, B-ultrasound has been used in the control of balloon dilation, and good clinical results have been initially achieved [20]. Further research found that direct visually controlled balloon dilation under cystoscopy can gently dilate the urethra with higher safety and efficacy [21].

Although balloon dilation is a well-tolerated minimally invasive endoluminal surgical procedure widely used in practice, its clinical significance has not been systematically and comprehensively reviewed. Our objective was to assess the efficacy and safety of balloon dilation and its associated influencing factors.

2. Materials and methods

2.1 Search strategy

This study followed the guidelines of the PRISMA statement [22] (Supplementary Table 1), and the specific protocol was registered on PROSPERO with the registration number CRD42022334403. Performing with Medical Subject Headings and free text terms, we searched the relevant records published prior to July 17, 2022 in the following databases: Medline, Embase, Cochrane Library, Web of Science and Scopus. The search strategy is shown in Supplementary File.

2.2 Eligibility criteria

Two researchers (X.L. and C.X.) screened and assessed the search results independently. The inclusion criteria included: (1) male patients diagnosed as urethral strictures; (2) balloon dilation was applied as the main intervention, not including patient self-dilation; (3) clinical studies about patients, retrospective or prospective; (4) report of the success rate and the rate of adverse events.

Conference abstracts were eligible for inclusion if they reported sufficient outcome data. If several articles were all related to the same study, the most recent publication with the most complete data was included in the systematic review. The consensus was finally reached through consultation and discussion in the event of any disagreement and differences between the two researchers.

2.3 Quality assessment

According to the type of study, the quality of included studies was independently assessed by two researchers (X.L. and C.X.). All observational studies were assessed using the Newcastle-Ottawa Scale (NOS) in terms of population selection, comparability, and outcome evaluation [23]. Randomized controlled trial (RCT) studies were assessed using the Jadad Quality Scale, and articles with the score >3 were considered as high-quality research [24]. For single-arm clinical trials, the first 8 items of the Methodological Index for Non-randomized Studies (MINORS) scale were used for assessment[25]. ROBINS-I tool was used to further assess the risk of bias in non-randomized controlled trial studies [26].

2.4 Data extraction

We extracted data on success rate, rate of adverse events, International Prostate Symptom Scores (IPSS), maximum uroflow (Qmax, mL/sec) and post-void residual urine volume (PVR). When disagreements arise, a third reviewer will participate in discussions and mediate to reach a consensus.

2.5 Statistics analysis

Stata 14.0 (StataCorp, USA) was applied for statistical analysis, reporting success rate and adverse effects rate as proportions. I^2 index was used to test the between-study heterogeneity. When $I^2 > 50\%$, it was considered significant heterogeneity and the

random effects model was used for pooled analysis, otherwise less heterogeneity was considered and the fixed effects model was used. By excluding any single study one by one, we performed a sensitivity analysis of balloon dilation success rate to assess the stability and reliability of the pooled result. Subgroup analyses were performed according to the results of meta-regression models.

2.6 Patient and public involvement

None.

3. Results

3.1 Study selection

The flowchart of the study retrieval process is shown in Figure 1. 15 studies were included for systematic review with a total of 842 patients. Table 1 and Table 2 present the main characteristics of the included studies. Of these, there are 1 randomized controlled trial (RCT) [27], 2 single-arm clinical trials [28, 29], 2 case-control studies [30, 31], and 10 retrospective case studies [32-41].

3.2 Quality analysis and risk of bias

We evaluated the quality of the 15 studies included in the systematic review, and the results are presented in Supplementary Table 2. Most of the current studies in this area are retrospective, with inadequate study designs and a lack of valid controls.

We further conducted a bias analysis of 14 non-randomized controlled trial studies using the ROBINS-I tool, and the evaluation criteria and results are shown in Supplementary Table 3. Since the operation is often influenced by the subjective preferences of the surgeons and most of the included studies are retrospective case studies, unavoidable selection bias is one of the most prominent issues. Selection bias is exacerbated in some small-sample studies of patients with specific comorbid conditions, such as coexisting urinary calculi. Some confounding factors such as age, body mass index, etiology, location of the stricture, length of stricture, prior intervention management, and others like patient baseline physical condition are present in most studies. Some of these confounding factors have not been appropriately controlled for in a multivariable-adjusted analysis. Some outcome measures of balloon dilation are subjective, and researchers may also exaggerate the efficacy of the balloon in order to publicize its advantages. Moreover, a funnel plot of eight studies included for the evaluation of conventional balloon dilation success rate was performed, and there is no evidence of publication bias (Egger test: $t=-2.42$, $p=0.052>0.05$) (Supplementary Figure 1). In addition, due to the small sample size of some of the included studies, there are certain limitations in reflecting the overall clinical situation.

3.3 The principle of balloon dilation

The principle of balloon expansion is to apply radial force along the balloon span at the stricture. While the principle of traditional optical internal urethrotomy is to

achieve epithelial regeneration by incising scar tissue. Compared with the parallel force brought by traditional rigid dilation, balloon dilation has less shear force and less trauma, which can reduce the risk of cavernous fibrosis and cause less discomfort [31, 42, 43]. Balloon dilation can also make the fibrous scar in the stricture more evenly fractured, presenting a 360° annular expansion, thereby increasing the inner diameter of the stenotic segment, and during the balloon dilation process, the urethral pressure gradually increases, and the expansion is slow and gentle, so as to avoid blood vessels due to violence [13]. Squeeze bleeding has the advantage of one-time expansion. In addition, the smooth balloon can avoid normal urethral mucosal damage.

3.4 Safety assessment and incidence of adverse events

Urinary tract infection, urinary retention and postoperative hematuria and dysuria are the main complications of balloon dilation. Therefore, strict aseptic and standardized operations are required during the surgical operation to prevent and avoid the occurrence of adverse events as much as possible.

We performed a pooled analysis of reported adverse event rates for urinary tract infection and urinary retention. The pooled incidence of infection in patients after balloon dilation is 3.27% (95% CI: 1.2%-8.86%; heterogeneity: I^2=46.2589%, p= 0.1338) (Supplementary Figure 2A). While, the pooled incidence of urinary retention was 8.31% (95% CI: 1.84%-18.39%; heterogeneity: I^2=84.6223%, p<0.05) (Supplementary Figure 2B). Urinary tract infection is the most common complication within 30 days of balloon dilation, and some patients require antibiotic treatment [32]. Some patients also have transient hematuria after surgery, but no further treatment such as blood transfusion is required [31, 32]. Furthermore, Yu, S. C.'s study also found that the incidence of major postoperative complications such as urethral bleeding and urinary tract infection in the balloon dilation group was lower than that in the DVIU group (urethral bleeding: 2/31 vs. 8/25, P=0.017; UTI: 1/31 vs. 6/25 P=0.037) [31].

3.5 Clinical efficacy of balloon dilation for male urethral strictures

3.5.1 Conventional balloon dilation success rate

For studies with conventional balloon dilation, we defined success of balloon dilation as no recurrence or no further stricture treatment during follow-up, excluding studies with a sample size of less than 30 on account of the potentially higher selection bias and merging data from 8 studies published in 2012-2022 [31, 32, 34-36, 38-40]. The pooled balloon dilation success rate was 67.07% (95% CI: 55.92%-77.36%; heterogeneity: I^2=86.8683%, p<0.05) (Figure 2A). This result needs to be taken with caution and most likely overestimates the efficacy of balloon dilation.

We performed a sensitivity analysis by excluding studies one by one. The recalculated results are shown in Supplementary Table 4 & Supplementary Figure 3. Compared to the pooled result of all studies, the maximum deviation rate is 5.3%, indicating that the final pooled result is relatively stable. We further did meta-regression and found that factors such as location of the stricture (t=5.25, $p < 0.05$), and length of the

stricture (t=7.97, p ＜0.05), age (t=7.97, p ＜0.05) may be associated with the high heterogeneity, and subgroup analyses of these factors were performed in the following contents of section 3.6.

3.5.2 Drug coated balloon dilation success rate

Balloons coated with drugs such as paclitaxel have achieved promising clinical results in recent years. Two studies on paclitaxel coated balloon in recurrent urethral stricture expressed its considerable effect on recurrent urethral stricture with relatively objective functional success rate (67%) and anatomical success rate (74.6%) [27, 28]. Functional success rate was defined as the percentage of subjects with ≥50% improvement in IPSS scores who did not require retreatment. Anatomical success rate was defined as the proportion of participants who could be atraumatically passed a 16Fr flexible cystoscope or a 14Fr catheter through the treated area at 6 months.

3.5.3 Assessment of patient's clinical symptoms

The changes in urinary flow rate, PVR, and IPSS scores of patients are summarized in Table 3. Compared with the preoperative condition, we found that the postoperative maximum urinary flow rate was greatly improved at 3 months (RR=2.6510, 95% CI: 1.0681-4.2338; z=3.282, p < 0.01; I^2=96.5%, p < 0.05), and the significant difference remained at one year postoperatively (RR=1.6637, 95% CI: 1.1837-2.1437; z=6.794, p < 0.01; I^2=78.8%, p < 0.05). The patient's IPSS scores and PVR also decreased accordingly.

Patients' subjective perception of improvement in voiding symptoms is a crucial indicator of the true efficacy of urethral stricture, and the concrete results are summarized in Table 4. The ROBUST III study [28] found that patients' International Prostate Symptom Score - Quality of Life (IPSS QoL) scores had risen significantly by 30 days after balloon dilation, with outstanding short-term efficacy. Moreover, three-year follow-up results from the ROBUST I trial study [27] indicated significant improvements in both QoL scores and Patient-Reported Outcome Measure for Urethral Stricture Surgery (USS-PROM) scores for patients with balloon dilation compared to baseline status (p<0.0001). With the extension of follow-up time, the quality of life of the patients remained at a good level, reflecting the long-term effectiveness of balloon dilation.

Table 1: The clinical characteristics and efficiency of balloon dilation (Ⅰ).

Study	Evaluable Patients (n)	Age (average)	Etiology	Location of the Strictures	Length of Stricture	Pre-dilated state
Virasoro, Ramon et al.	43	50.7 (22.0 - 81.0)	/	Anterior urethra	≤ 2 cm	1–4 prior endoscopic treatments (none within 3 months of enrollment)

Elliott, S. P. et al.	60 (79): 15 (48)*	60.6 ± 16.0 : 58.7 ± 15.5	Iatrogenic (21/78, 26.9%); Idiopathic (42/78, 53.8%); Inflammatory (1/78, 1.3%); Traumatic (14/78, 17.9%); pelvic radiation (9/79, 11.4%)	Anterior urethra	≤ 3 cm	≥ 2 prior endoscopic treatments
Beeder, L. A. et al.	91	61	/	Anterior urethra (n=75, 82%); posterior urethra (n=16, 18%)	/	Most (75/91, 82%) had prior treatment for USD (endoscopic 50/91 (55%), 51/91 (56%) urethroplasty)
Alibekov, M. M. et al.	7	52 (47 - 65)	Idiopathic (4/7, 57.1%); Inflammatory (1/7, 14.3%); Traumatic (2/7, 28.6%)	Anterior urethra	≤ 1 cm	All patients had 1 urethral stone. The sizes of the stone ranged from 4 to 9 mm (median - 6 mm)
Yi, Y. A. et al.	80	/	/	Anterior urethra (n=59, 74%); posterior urethra (n=21, 26%)	≤ 1.5 cm	Over 75% of patients had some form of prior stricture treatment, including dilation (34/80, 42.5%), DVIU (19/80, 23.8%), or urethroplasty (48/80, 60%)
Kumano, Y. et al.	13 : 9	71 : 63	Iatrogenic (10/13, 76.9%); Idiopathic (3/13, 23.1%)	Anterior urethra (n=9, 41%); posterior urethra (n=13, 59%)	/	/
Zhou, Y. et al.	45	46.6 (22 - 76)	Iatrogenic (19/45, 42.2%); Inflammatory (5/45, 11.1%); Traumatic (18/45, 40%); pelvic radiation (3/45, 6.7%)	Anterior urethra (n=36, 80%); posterior urethra (n=9, 20%)	≤ 2 cm	5 patients had a prior suprapubic cystostomy
Yu, S. C. et al.	31 : 25	49 (32 - 67) : 44 (24 - 71)	Iatrogenic (7/31, 22.6%); Idiopathic (1/31, 3.2%); Inflammatory (2/31, 6.5%); Traumatic (21/31, 67.7%);	Anterior urethra (n=45, 80%); posterior urethra (n=11, 20%)	≤ 1 cm (n=48, 86%) ; > 1 cm (n=8, 14%)	None received prior endovascular therapy
Chhabra, J. S. et al.	134 (144)*	52 (18 - 85)	Iatrogenic (59/144, 41.0%); Idiopathic (84/144, 58.3%); pelvic radiation (1/144, 0.7%)	Anterior urethra (n=110, 76%); posterior urethra (n=8, 6%); both (n=26, 18%)	≤ 1.5 cm (n=130, 90%) ; > 1 cm (n=14, 10%)	/
Ishii, Gen et al.	10	70 (61 - 75)	Iatrogenic	Posterior urethra	/	All patients had cystourethral anastomotic stricture after radical prostatectomy
Mao, D. et al.	37 (39)*	55 (24 - 84)	/	Anterior urethra (n=17, 44%); posterior urethra (n=20, 51%); both	≤ 2 cm	/

				(n=2, 5%)		
Vyas, J. B. et al.	120	49.86 (30 - 85)	/	Anterior urethra (n=114, 95%); posterior urethra (n=6, 5%)	≤ 1.5 cm	/
Alguersuari, A. et al.	65	63.17 ± 16.9	/	Anterior urethra (26.2%); posterior urethra (73.8%)	≤ 2 cm (86.2%) ; > 2 cm (13.8%)	/
MacDiarmid, S. A. et al.	51	/	Iatrogenic (27/51, 52.9%); Idiopathic (11/51, 21.6%); Inflammatory (10/51, 19.6%); Traumatic (3/51, 5.9%)	Anterior urethra (n=49, 96%); posterior urethra (n=2, 4%)	/	/
Mohammed, S. H. et al.	6 (7)*	35 (16 - 67)	Iatrogenic (1/6, 16.7%); Idiopathic (2/6, 33.3%); Inflammatory (2/6, 33.3%); Traumatic (1/6, 16.7%)	Anterior urethra (n=4, 57%); posterior urethra (n=3, 43%)	/	/

* In parentheses are the number of people who were initially assessed at baseline in the study, and outside brackets were the number of people who could be effectively assessed at the end of the follow-up.

Table 2: The clinical characteristics and efficiency of balloon dilation (Ⅱ).

Study	Balloon Types	Control	Definition of Success Rate	Reported Success Rate (%)	Follow-up
Virasoro, Ramon et al.	Optilume® drug coated balloon (DCB)	/	Functional success was defined as ≥50% reduction in International Prostate Symptom Score (IPSS) without need for retreatment.	67	3 years
Elliott, S. P. et al.	Optilume® drug coated balloon (DCB)	dilation / DVIU	Anatomical success: the proportion of participants in whom the surgeons could atraumatically pass a 16-French flexible cystoscope or a 14-French catheter through the treated area at 6 months	74.6 : 26.8	1 year
Beeder, L. A. et al.	8-cm, 24-French UroMax Ultra™ balloon dilator	/	Proportion of patients who reported no recurrence of lower urinary tract symptoms or did not need further stricture treatment	50	12 months (3 - 40)
Alibekov, M. M. et al.	/	/	Proportion of patients without recurrence of urethral stricture after 18 months of dilation	85.7	14 months (3 - 24)
Yi, Y. A. et al.	8-cm, 24-French UroMax Ultra™ balloon dilator	/	Proportion of patients with postoperative urethral stricture who did not recur or did not need further stricture treatment	66.3	8.4 months (IQR, 3.9 - 22.5)
Kumano, Y. et al.	Balloon dilation catheter (X-FORCE; BARD Medical,	OIU	Proportion of patients with no recurrence of stricture during the follow-up period	84 : 22	/

	Murray Hill, NJ, USA)				
Zhou, Y. et al.	Balloon catheter (X-Force™, C.R. Bard Inc., USA)	/	Proportion of patients without further stricture treatment during the follow-up period	86.7	6 - 24 months
Yu, S. C. et al.	6-cm, 7-French balloon catheter (X-Force™, C.R. Bard Inc., USA)	DVIU	Proportion of patients with postoperative urethral stricture who did not recur or did not need further stricture treatment	35.5	14.75 months (5 - 36)
Chhabra, J. S. et al.	8-cm, 24-French urethral Balloon catheter set (Cook Urological, Spencer, Ind., USA)	/	Proportion of patients without further stricture treatment during the follow-up period	84.4	24 months (3 - 52)
Ishii, Gen et al.	6-cm, 6-French Balloon catheter, the X Force®	/	Proportion of patients with no recurrence of strictureduring the follow-up period	80	24 months (7 - 67)
Mao, D. et al.	24-French Nephrostomy balloon dilation catheter, the X Force®	/	Proportion of patients without further stricture treatment during the follow-up period	64.9	/
Vyas, J. B. et al.	8-cm, 24-French urethral Balloon catheter set (Cook Urological, Spencer, Ind., USA)	/	Proportion of patients without further stricture treatment during the follow-up period	68	6 months (2 - 60)
Alguersuari, A. et al.	fluoroscopic- guided balloon dilation	/	Proportion of patients without further stricture treatment during the follow-up period	69	/
MacDiarmid, S. A. et al.	The UrethraMax (4, 6, or 8-cm; 24-French) or a coude tip balloon dilation catheter	/	Proportion of patients without further stricture treatment during the follow-up period	55	9 months (1 - 16)
Mohammed, S. H. et al.	Olbert balloon catheter	/	Proportion of patients without further stricture treatment during the follow-up period	66.7	12 months (6 - 26)

DVIU, direct vision internal urethrotomy; OIU, optical internal urethrotomy.

Table 3: Changes in urinary flow rate, PVR, and IPSS scores of patients after balloon dilation. (The following table is continued to the right)

Study	Location of the Strictures	Length of Strictures
Virasoro, Ramon et al. 2022	Anterior urethra	≤ 2 cm
Elliott, S. P. et al. 2022	Anterior urethra	≤ 3 cm
Zhou, Y. et al. 2016	Anterior urethra (n=36, 80%);	≤ 2 cm

	posterior urethra (n=9, 20%)	
Chhabra, J. S. et al. 2016	Anterior urethra (n=110, 76%); posterior urethra (n=8, 6%); both (n=26, 18%)	≤ 1.5 cm (n=130, 90%) ; > 1 cm (n=14, 10%)
Vyas, J. B. et al. 2013	Anterior urethra (n=114, 95%); posterior urethra (n=6, 5%)	≤ 1.5 cm
MacDiarmid, S. A. et al. 2000	Anterior urethra (n=49, 96%); posterior urethra (n=2, 4%)	/

IPSS					
Before surgery	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
25.2 ± 4.5 （n=53)	6.1 ± 7.6 (n=51)	4.6 ± 5.2 (n=45)	4.5 ± 3.9 (n=40)	6.9 ± 7.7 (n=38)	5.5 ± 6.9 (n=33)
22.0 ± 6.8 （n=79)	7.4 ± 5.8 (n=74)	8.3 ± 6.2 (n=71)	9.0 ± 7.1 (n=67)	/	/
/	/	/	/	/	/
/	/	12.7 (n=112)	12.6 (n=112)	/	/
21.6 (n=120)	11.4 (n=120)	12.6 (n=120)	/	/	/
/	/	/	/	/	/
Qmax (mL/sec)					
Before surgery	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
5.0 ± 2.6 (n=46)	22.2 ± 12.5 (n=51)	19.8 ± 10.8 (n=45)	20.1 ± 10.0 (n=39)	17.5 ± 10.4 (n=38)	15.1 ± 8.3 (n=33)
7.6 ± 3.4 (n=78)	18.6 ± 10.9 (n=71)	16.6 ± 8.9 (n=69)	15.5 ± 9.0 (n=65)	/	/
5.6 ± 1.4 (n=45)	19.8 ± 3.9 (n=45)	/	/	/	/
5.2 ± 2.7 (n=144)	/	15.4 ± 7.2 (n=112)	12.6 ± 5.7 (n=112)	/	/
5.7 (n=120)	14.3 (n=120)	12.7 (n=120)	/	/	/
10.4 (n=48)	15.3 (n=43)	17.7 (n=27)	15.2 (n=5)	/	/

PVR (mL)					
Before surgery	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
141.4 ± 105.1 (n=43)	141.4 ± 105.1 (n=51)	30.0 ± 42.8 (n=45)	24.6 ± 32.1 (n=39)	45.5 ± 49.5 (n=38)	50.2 ± 62.5 (n=33)
109.8 ± 116.9 (n=77)	103.4 ± 134.4 (n=70)	73.1 ± 117.7 (n=67)	94.6 ± 121.8 (n=66)	/	/
/	/	/	/	/	/
/	/	/	/	/	/
90.2 (n=120)	34.2 (n=120)	20.2 (n=120)	/	/	/
/	/	/	/	/	/

IPSS, International Prostate Symptom Scores; Qmax, maximum uroflow; PVR, post-void residual urine volume.

Table 4: Changes in USS-PROM, IPSS QOL, and IIEF scores of patients after balloon dilation.

Study: Virasoro, Ramon et al. 2022						
Scoring items	**Before surgery**	**3 months**	**6 months**	**1 year**	**2 year**	**3 year**
USS-PROM	15.9 ± 4.7 (n=53)	3.2 ± 5.5 (n=51)	1.9 ± 2.9 (n=45)	1.4 ± 1.8 (n=40)	3.6 ± 5.8 (n=38)	2.0 ± 3.5 (n=33)
IPSS QoL	4.9 ± 0.9 (n=53)	0.8 ± 1.3 (n=51)	0.7 ± 0.9 (n=45)	0.7 ± 0.9 (n=40)	0.9 ± 1.5 (n=38)	0.7 ± 1.2 (n=33)
IIEF - OS	6.5 ± 2.6 (n=53)	7.9 ± 2.5 (n=51)	7.9 ± 2.5 (n=45)	8.1 ± 2.5 (n=40)	7.6 ± 2.5 (n=38)	8.2 ± 2.2 (n=33)
IIEF - EF	16.0 ± 12.2 (n=53)	20.7 ± 12.0 (n=51)	21.0 ± 11.8 (n=45)	22.1 ± 10.9 (n=40)	21.1 ± 11.9 (n=38)	22.5 ± 11.2 (n=33)
Study: Elliott, S. P. et al. 2022						
Scoring items	**Before surgery**	**30 days**	**3 months**	**6 months**	**1 year**	/
IPSS QoL	4.5 ± 1.3 (n=79)	1.7 ± 1.4 (n=78)	1.6 ± 1.4 (n=74)	1.7 ± 1.3 (n=71)	1.9 ± 1.5 (n=67)	/
IIEF	5.8 ± 2.9 (n=72)	5.9 ± 2.8 (n=75)	6.6 ± 2.7 (n=71)	6.5 ± 2.8 (n=68)	6.9 ± 3.0 (n=59)	/

USS-PROM, Patient-Reported Outcome Measure for Urethral Stricture Surgery; IPSS QoL, International Prostate Symptom Score - Quality of Life; IIEF, International Index of Erectile Function; IIEF – OS, International Index of Erectile Function – overall satisfaction domain; IIEF – EF, International Index of Erectile Function – erectile function domain.

3.5.4 Comparison of balloon dilation with other endoluminal treatments

We conducted a separate analysis of two studies compared with DVIU and optical internal urethrotomy (OIU), finding no statistically significant difference in efficacy between conventional balloon dilation and internal urethrotomy (RR=1.4754, 95%CI: 0.7306-2.9793; z=1.085, p=0.278; heterogeneity: I^2=0%, p=0.351) (Figure 2B). The study by Yu, S. C. et al found the estimated stricture-free rate at 12 months was 77.42% after balloon dilation and 48.00% after DVIU, which showed a significantly higher stricture-free survival in the balloon dilation group (P=0.02<0.05, HR=0.35, 95% CI for HR: 0.14–0.87) [31]. In Kumano, Y.'s study, the balloon dilation group had significantly longer stricture-free times than optical internal urethrotomy (p<0.01), with median (mean) stricture -free times of 1675 (1673) and 244 (599) days, respectively [30]. For the time being, there are no studies comparing the clinical outcomes of simple dilation versus balloon dilation. Although there is insufficient evidence to suggest that balloon dilation is superior to other conventional endoluminal therapies, balloon dilation may have a longer stricture -free time

3.6 Clinical preference and efficacy influencing factors of balloon dilation

3.6.1 Etiology

We pooled eight studies of simple balloon dilation that addressed specific etiologies [29-31, 33, 35-37, 41], involving a total of 307 patients. Iatrogenic urethral strictures (43.32%, 133/307) and idiopathic urethral strictures (34.20%, 105/307) accounted for the vast majority. The stricture caused by trauma and inflammation accounted for 14.66% (45/307) and 6.51% (20/307) respectively. There were also 4 patients suffering from radiation. Although this is only a one-sided epitome, it follows the trend that iatrogenic injury may become the main etiology of urethral stricture in males in the future.

Due to the lack of meticulous subgroup analysis in the included literatures, it is difficult for us to directly compare the efficacy difference among strictures caused by different etiologies. The influence of etiology on the efficacy of balloon dilation depends primarily on the type of stenotic pathology it creates and the specific stenotic segment length and location. The essence of balloon dilation is the expansion of physical properties, which needs to avoid the re fibrosis of scar tissue in the narrow segment to the greatest extent. Once the process of re-fibrosis progresses, strictures are highly likely to recur. Therefore, balloon dilation may not perform well for strictures with high degree of fibrosis. Lichen sclerosus is a specific cause of urethral strictures. The narrow segment pathologic features of lichen sclerosus include hyperkeratosis or epithelial atrophy, basal cell vacuolar degeneration, lichenoid lymphocytic infiltration, and upper epithelial sclerosis [44]. This epithelial stromal

lesion characterized by squamous atrophy or hyperplasia is distinct from the fibrotic pathologic characterization of most urethral strictures. A recent review pooling expert opinion in urology stated dilation is unlikely to be a successful long-term solution for lichenoid sclerosing urethral stricture, potentially triggering longer adverse outcomes [45]. Balloon dilation is essentially a physical treatment, which is difficult to pathologically and fundamentally improve the condition of patients with specific urethral strictures, and its clinical indications need to be strictly controlled..

3.6.2 Location of urethral stricture

We combined 11 studies that identified the location of stricture [29, 32-41]. The patients with anterior urethral stricture accounted for 74.28% (488/657), the patients with posterior urethral stricture accounted for 21.77% (143/657), and 3.95% (26/657) patients had both strictures. The majority of patients receiving balloon dilation are patients with anterior urethral stricture, since its high incidence rate.

Most of the current studies have not further categorized comparisons of balloon dilation based on differences in stricture location, and cases with different stricture sites were analyzed together. A subgroup analysis of eight conventional balloon dilation studies that were involved in the combination of success rate previously [31, 32, 34-36, 38-40] was performed according to the percentage of anterior urethral strictures, and the results are shown in Supplementary Figure 4. The combined results of studies dominated by anterior urethral strictures (70%-90%) indicated a success rate of 66.45% (95% CI: 47.58%-83.01%) for balloon dilation.

Moreover, we combined data from two studies [32, 34] that performed subgroup analysis of stricture location and did not find any statistical difference in the efficacy of balloon dilation between anterior and posterior urethral strictures (RR=0.9568, 95%CI: 0.6618-1.3832, p=0.814) (Figure 3A).

3.6.3 Length of urethral stricture

We performed a subgroup analysis of pooled conventional balloon dilation success rate previously [31, 32, 34-36, 38-40] due to the length of urethral stricture, and the results are shown in Figure 3B. In shorter strictures (≤ 2cm), the success rate of balloon dilation was up to 71.58% (95% CI: 61.93%-80.35%), and heterogeneity was also reduced (I^2=63.2342%, $p < 0.05$) (Figure 3B). In a study of patients with anterior urethral strictures of less than 1 cm in length, the success rate was as high as 85.7% [33]. The reduction in heterogeneity of the pooled results suggests that the stenotic segment length is a prognostic factor, and balloon dilation may have a higher success rate in short segment urethral strictures.

3.6.4 Age

We further stratified the previous eight studies [31, 32, 34-36, 38-40] on account of different age groups, the results were shown in Figure 3C. In the age group of 50 to 60 years, the success rate of balloon dilation was 80.79% (95% CI: 74.42%-86.47%). However, when the patients were over 60 years old, the success rate dropped to 58.49% (95% CI: 50.61%-66.17%). Interestingly, the combined success rate was at

65.39% (95% CI: 39.61%-87.22%) in relatively young patients, probably because part of the reported younger patient had a more severe stricture. The etiology of strictures in elderly patients is often iatrogenic, whereas in younger patients more complex urethral strictures can be caused by relatively specific factors such as trauma and lichenoid sclerosis gonorrhea. Even though the success rate is somewhat subjective, we can roughly see the decreasing trend of the efficacy of balloon dilation in elderly patients.

3.6.5 Prior intervention management

A separate analysis of patients who had received prior endoscopic management (catheter/balloon dilation, direct visual internal urethrotomy) in two studies [32, 34] was performed and we found that balloon dilation had a pooled success rate of 49.51% (95% CI: 39.79%-59.26%) (Figure 3D). In patients with previous surgical intervention, the efficacy of balloon dilation may be diminished. Based on the limited data available in these two studies [32, 34], we compared patients with and without previous urethroplasty, and found no statistical difference in the success rate of conventional balloon dilation (RR=1.1682, 95%CI: 0.6160-2.2153, p=0.634) (Supplementary Figure 5A). The prevailing clinical view is that repeated endoluminal intervention may render further endoluminal treatment less effective, but this needs to be confirmed by clinical studies with larger sample sizes.

3.6.6 Other patient status

We performed a more nuanced subgroup analysis of the two studies [32, 34] that provided some patient baseline details. There was no statistically significant difference in balloon dilation efficacy between patients with a history of smoking and non-smoking patients (RR=1.1052, 95%CI: 0.8083-1.5112, p=0.531) (Supplementary Figure 5B). Chronic diseases such as coronary artery disease (RR=1.0714, 95%CI: 0.7618-1.5069, p=0.692), diabetes mellitus (RR=0.9144, 95%CI: 0.6118-1.3666, p=0.662), hypertension (RR=0.8377, 95%CI: 0.6121-1.1464, p=0.269), and chronic obstructive pulmonary disease (RR=1.3515, 95%CI: 0.7495-2.4374, p=0.317) also did not show statistical differences in the efficacy of balloon dilation (Supplementary Figure 5C-F). Our preliminary analysis results suggest that patient status such as poor living habits and chronic diseases may not have a significant impact on the efficacy of balloon dilation.

3.7 Intermittent urethral balloon self-dilation

Patient self-balloon dilation is a specific form of balloon dilation, and we also briefly review its clinical evaluation. Urethral dilation is easy to perform and can be performed by the patient at home, avoiding repeated hospitalizations and frequent general anesthesia [46]. A study by Levine, L. A. [47] suggests that adjuvant home balloon self-dilation may be a potential option for patients at high risk of recurrence. In this study of 25 evaluable patients, the majority of patients noted that balloon dilation improved voiding and maintained or improved peak urinary flow rate at an average of 18.7 months of long-term follow-up. Nonetheless, six patients (19%)

complained of balloon placement discomfort, 3 (10%) noted minor bleeding during dilation, and 4 (13%) developed urinary tract infections during follow-up. Hennessey, D. B.'s initial experience with self-expanding balloon dilation in the outpatient setting was encouraging, with all 11 patients reporting that they were very satisfied or satisfied with overall outcomes and quality of life [48]. A recent study reported in 2021 stated that the self-urethral balloon dilation offers patients with complex strictures, especially those with a history of radiation, an opportunity to avoid surgical intervention [49].

However, due to the imprecision of patient self-balloon dilation, which may cause complications and even aggravate injury. As early as the last century, scholars have shown that short-term postoperative self-dilation techniques do not appear to prevent recurrence of strictures in patients treated with endourethral incisions [50]. A recent meta-analysis of patient self-dilation also indicated that the quality of evidence for this approach to reduce the risk of recurrent urethral strictures is very low [51]. Although self-dilation is very convenient and avoids the complications of surgery, it is not suitable for all patients, and not all patients can master the skills and techniques of dilation. Self-balloon dilation by the patient needs to be further weighed against surgery, and well-designed randomized controlled trials are needed to determine whether this benefit of convenience is sufficient to make this intervention worthwhile.

4. Discussion

With the gradual increase of iatrogenic urethral strictures, the surgeon should choose the appropriate treatment method according to the etiology of the urethral stricture, the location and length of the stricture, and the degree of urethral fibrosis.

Even though there is no clear evidence that the clinical efficacy of balloon dilation is significantly better than that of other endoluminal treatments, balloon dilation still has a large clinical plasticity.

Both balloon dilation and simple dilation are essentially dilatation, a tearing of scar tissue and scar remodeling at the site of the stricture. Balloon dilation applies a 360° circumferential radial force at the stricture site, providing a more uniform force than simple dilation. Meanwhile, for some harder scars that cannot be torn by simple dilation, the balloon can gradually increase the pressure to achieve the purpose of dilatation, which has a broader clinical indications.

Urethrotomy leads to a radial incision at the site of the stricture. The study by Yu, S. C. et al found that the balloon dilation operation time was much shorter than DVIU [(13.19±2.68) min vs (18.44±3.29) min, $P<0.01$] [31], highlighting the operational simplicity of balloon dilation. The main disadvantage of internal urethrotomy is the inability to accurately estimate the depth of scar tissue during the procedure, resulting in imprecise scar tissue incisions. There may also be damage to the corpus cavernosum below the urethra, and vascular disruption in the corpus cavernosum and localized extravasation of urine through mucosal fissures may exacerbate corpus cavernosum fibrosis, eventually leading to recurrence of strictures [31, 52]. Some scholars believe that balloon dilation tends to be performed in less fibrotic cases

without urethral cavernous fibrosis, speculating that the role of balloon dilation will not invade the deep urethral membrane, therefore, even if the dilation time is longer, the restenosis rate of balloon dilation is lower than optical internal urethrotomy [30]. Thus, DVIU is commonly used for posterior urethral strictures and is avoided in the penile urethra to prevent leakage of the cavernous penile veins to circumvent the risk of causing impotence. Balloon dilation has no definitive stricture site limitations and can be effective in the dilatation of hard-textured scars that cannot be incised by DVIU.

The advent and use of drug-coated balloons can reduce inflammation and reduce relapse rates by releasing drugs such as immunosuppressants while expanding. Barbalias, D. et al conducted animal experiments using paclitaxel-coated balloons and found that paclitaxel could break through the urothelial barrier and immediately distribute to the urothelium, submucosa and smooth muscle layers of the normal rabbit urethra after dilation [53]. The drug can penetrate the epithelium and act on the deep urethral tissue, effectively reduce inflammation and inhibit urethral fibrosis. In the recent ROBUST I study [28], Optilume drug coated balloon (DCB) maintained symptomatic improvement for 3 years after treatment in a highly susceptible population with recurrent urethral strictures. The 43 patients in this trial had a functional success rate of 67%, a retreatment-free rate of 77%, and an improvement in mean IPSS from 25.2 at baseline to 5.5 at 3 years ($p<0.0001$). One-year results from another RCT (ROBUST Ⅲ study) [27] showed that Optilume DCB had a significantly higher anatomicalsuccess rate at 6 months than the DVIU group (75% vs 27%, $p<0.001$). Immediate symptoms and urinary flow rates were significantly improved in both groups, but the effects were significantly more durable in the Optilume DCB group. The United States Food and Drug Administration (FDA) has approved the Optilume Device for the treatment of male urethral strictures [54]. Nevertheless, in the ROBUST III study [27], the incidence of serious adverse events in the control group (DVIU / simple dilation) and DCB group was 16.7% and 10.1%, respectively. The types and incidence of adverse events in the two groups were very matched, but the incidence of postoperative hematuria and dysuria was higher in the DCB group than in the control group (11.4% and 2.1% for both event types, respectively). Besides, Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation is expected to delay stricture recurrence in patients with urethral strictures. A clinical report of five patients found that the mean treatment interval was prolonged from 2.2 months to 10.7 months after Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation [55]. The design of new balloons such as cutting balloons and the exploration of some new expansion techniques may be another important direction in the future [56, 57]. The new type of balloon should meet the biomechanical requirements to better fit the narrow urethra.

Although urethroplasty is considered the most recommended treatment for urethral strictures, balloon dilation can also be widely used clinically due to its simplicity and economy. Compared with urethrotomy, balloon dilation has a lower cost and can improve the efficiency of clinical turnover [58]. The timing of balloon dilation is closely related to the location, length, and scar thickness of the stricture, and

appropriate case selection is critical. Balloon dilation is particularly suitable for patients with urethral strictures <1 cm in length, especially bulbar urethral strictures. In patients with recurrent strictures, the treatment strategy of initial urethrotomy or urethral dilation followed by urethroplasty has been shown to be the most cost-effective strategy [59]. Balloon dilation may provide an intermediate step before urethroplasty, as well as a promising alternative therapy to simple dilation and urethrotomy. As for some patients with long segments of complex urethral strictures, balloon dilation may even be used as an initial therapeutic attempt. The use of endoscopic urethroplasty combined with balloon dilation for traumatic destruction of the prostatic membranous urethra has been previously reported [60]. Balloon dilatation can also be used in conjunction with repeat simple dilation, endourethrotomy and urethroplasty, suggesting that it may be an important intermediate choice for the treatment of male urethral stricture.

We recognize the limitations of our research. There is considerable risk of bias in this meta-analysis, most of which stemmed from the retrospective design of the studies and the lack of valid controls. Interpretation of evidence from retrospective observational studies needs to be approached with caution on account of the susceptibility to selection bias, recall bias, and exaggerated efficacy of balloon dilation. The assessment of the efficacy of balloon dilation is often subjective, and it is difficult to have a clear objective criterion. Different patients have different perceptions of their voiding status, and the patient's subjective feelings can influence their choice of therapeutic intervention. The efficacy of balloon dilation is also affected by confounding factors such as etiology, stricture location, stricture length, prior intervention management, comorbidities and socio-economic status. Long- term outcomes of balloon dilation need to be further refined. RCTs with better design, larger sample sizes, and more comparable control groups are needed to further illustrate the efficacy and safety of balloon dilation in the future.

Contribution Statement

Conceptualization was created by X.L and C.X. Investigation was performed by X.L, X.J, and C.X. Analysis and interpretation of data were produced by X.L, X.J and C.X. X.L and C.X wrote the manuscript. X.L and X.J conducted the statistical analysis. Critical revision of the manuscript for important intellectual content was produced by X.L, C.X, Z.Z, T.C, Z.G and J.L. Supervision was performed by J.L.

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None.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Statement of Ethics

The outcome of this meta-analysis could improve clinical decision and help to reduce the risk and cost of patients. All patients included in this study have signed informed consent during the course of each trial. And specific methods of assessment in each trial have been illustrated above. This systematic review did not any addition intervention to all included individuals. Thanks to all the patients and researchers included for their contribution to this study.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Figure 1: Flow diagram of study selection.

Figure 2: Forest plots showing the efficacy of balloon dilation. (A) Success rate of simple balloon dilation; (B) Balloon dilation (Drug-coated balloons excluded) compared with simple dilation, DVIU, and optical internal urethrotomy (OIU). CI, confidence interval.

Figure 3: Forest plots showing the possible influencing factors of balloon dilation. (A) Location of urethral stricture; (B) Length of urethral stricture; (C) Age; (D) Prior endoscopic management. CI, confidence interval.

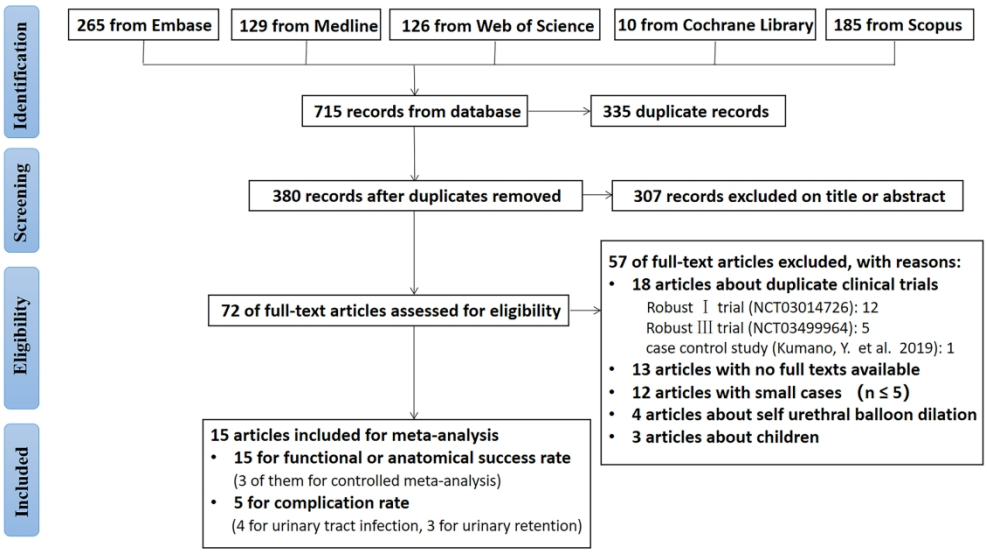

Figure 1: Flow diagram of study selection.

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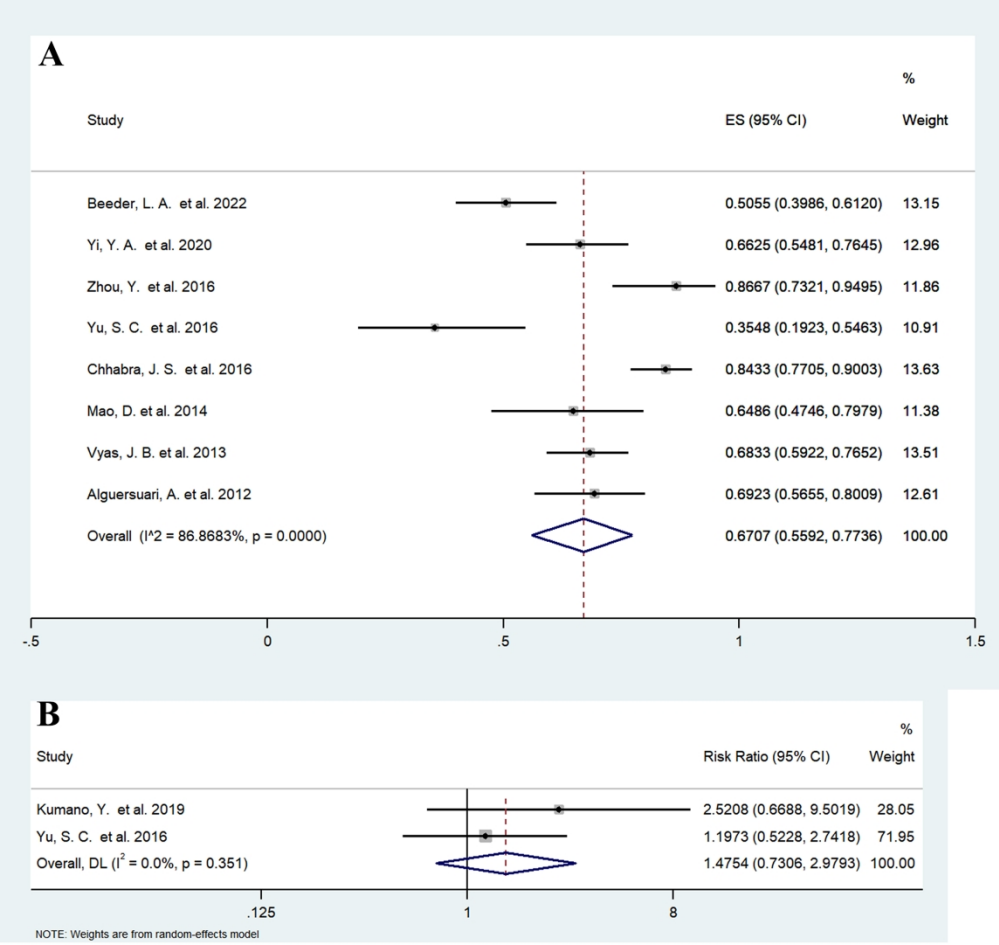


Figure 2: Forest plots showing the efficacy of balloon dilation. (A) Success rate of simple balloon dilation; (B) Balloon dilation (Drug-coated balloons excluded) compared with simple dilation, DVIU, and optical internal urethrotomy (OIU). CI, confidence interval.

209x198mm (300 x 300 DPI)

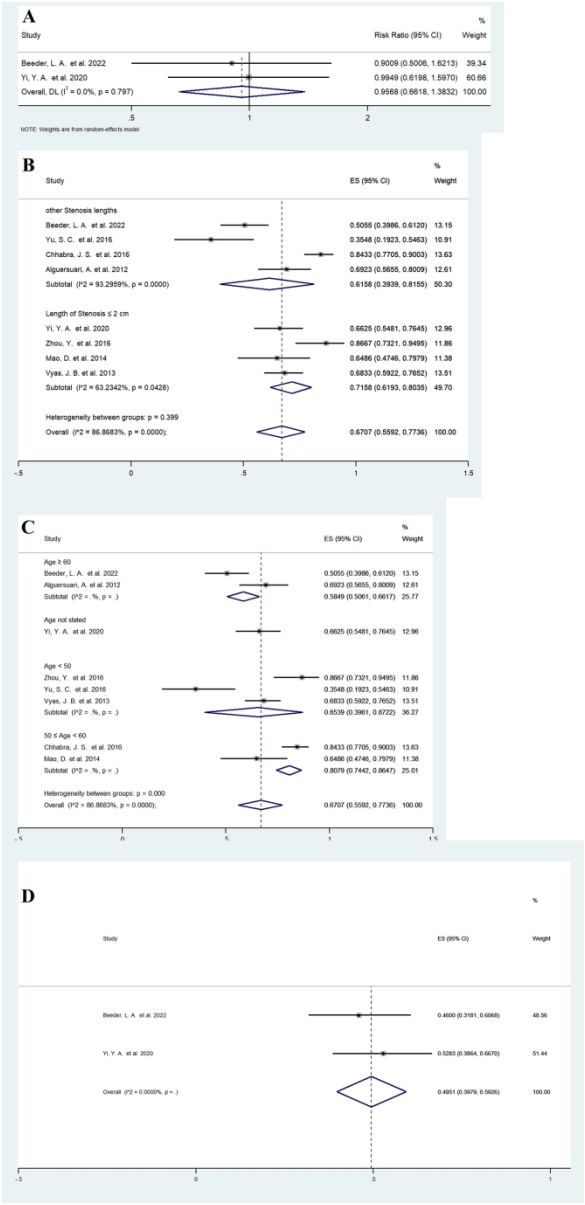


Figure 3: Forest plots showing the possible influencing factors of balloon dilation. (A) Location of urethral stricture; (B) Length of urethral stricture; (C) Age; (D) Prior endoscopic management. CI, confidence interval.

144x297mm (300 x 300 DPI)

Supplementary File. Search strategy

(Urethral Stricture OR Stricture, Urethral OR Strictures, Urethral OR Urethral Strictures OR Urethral Stenosis OR Stenoses, Urethral OR Stenosis, Urethral OR Urethral Stenoses OR Anterior Urethral Stricture OR Anterior Urethral Strictures OR Urethral Strictures, Anterior OR Urethral Stricture, Anterior OR Posterior Urethral Stricture OR Posterior Urethral Strictures OR Urethral Strictures, Posterior OR Urethral Stricture, Posterior) AND (Dilatation OR Dilatations OR Dilation OR Dilations) AND (Balloon)

MEDLINE

#1. TS=(Urethral Stricture OR Stricture, Urethral OR Strictures, Urethral OR Urethral Strictures OR Urethral Stenosis OR Stenoses, Urethral OR Stenosis, Urethral OR Urethral Stenoses OR Anterior Urethral Stricture OR Anterior Urethral Strictures OR Urethral Strictures, Anterior OR Urethral Stricture, Anterior OR Posterior Urethral Stricture OR Posterior Urethral Strictures OR Urethral Strictures, Posterior OR Urethral Stricture, Posterior)

#2. TS=(Dilatation OR Dilatations OR Dilation OR Dilations)

#3. TS=(Balloon)

#1 AND #2 AND #3

Web of Science (WOS)

#1. TS=(Urethral Stricture OR Stricture, Urethral OR Strictures, Urethral OR Urethral Strictures OR Urethral Stenosis OR Stenoses, Urethral OR Stenosis, Urethral OR Urethral Stenoses OR Anterior Urethral Stricture OR Anterior Urethral Strictures OR Urethral Strictures, Anterior OR Urethral Stricture, Anterior OR Posterior Urethral Stricture OR Posterior Urethral Strictures OR Urethral Strictures, Posterior OR Urethral Stricture, Posterior)

#2. TS=(Dilatation OR Dilatations OR Dilation OR Dilations)

#3. TS=(Balloon)

#1 AND #2 AND #3

EMBASE

#1. 'Stricture, Urethral':ab,ti OR 'Strictures, Urethral':ab,ti OR 'Urethral Strictures':ab,ti OR 'Urethral Stenosis':ab,ti OR 'Stenoses, Urethral':ab,ti OR 'Stenosis, Urethral':ab,ti OR 'Urethral Stenoses':ab,ti OR 'Anterior Urethral Stricture':ab,ti OR 'Anterior Urethral Strictures':ab,ti OR 'Urethral Strictures, Anterior':ab,ti OR 'Urethral Stricture, Anterior':ab,ti OR 'Posterior Urethral Stricture':ab,ti OR 'Posterior Urethral Strictures':ab,ti OR 'Urethral Strictures, Posterior':ab,ti OR 'Urethral Stricture, Posterior':ab,ti

#2. 'Dilatation':ab,ti OR 'Dilatations':ab,ti OR 'Dilation':ab,ti OR 'Dilations':ab,ti

#3. 'Balloon':ab,ti

#1 AND #2 AND #3

Cochrane Library

#1. (Urethral Stricture):ti,ab OR (Strictures, Urethral):ti,ab OR (Stricture, Urethral):ti,ab OR (Urethral Strictures):ti,ab OR (Urethral Stenosis):ti,ab OR (Stenoses, Urethral):ti,ab OR (Stenosis, Urethral):ti,ab OR (Urethral Stenoses):ti,ab OR (Anterior Urethral Stricture):ti,ab OR (Anterior

Urethral Strictures):ti,ab OR (Urethral Strictures, Anterior):ti,ab OR (Urethral Stricture, Anterior):ti,ab OR (Posterior Urethral Stricture):ti,ab OR (Posterior Urethral Strictures):ti,ab OR (Urethral Strictures, Posterior):ti,ab OR (Urethral Stricture, Posterior):ti,ab
#2. (Dilatations):ti,ab OR (Dilatation):ti,ab OR (Dilation):ti,ab OR (Dilations):ti,ab
#3. (Balloon):ti,ab
#1 AND #2 AND #3

Scopus
#1. TITLE-ABS-KEY("Urethral Stricture" OR "Stricture, Urethral" OR "Strictures, Urethral" OR "Urethral Strictures" OR "Urethral Stenosis" OR "Stenoses, Urethral" OR "Stenosis, Urethral" OR "Urethral Stenoses" OR "Anterior Urethral Stricture" OR "Anterior Urethral Strictures" OR "Urethral Strictures, Anterior" OR "Urethral Stricture, Anterior" OR "Posterior Urethral Stricture" OR "Posterior Urethral Strictures" OR "Urethral Strictures, Posterior" OR "Urethral Stricture, Posterior")
#2. TITLE-ABS-KEY("Dilatation" OR "Dilatations" OR "Dilation" OR "Dilations")
#3. TITLE-ABS-KEY("Balloon")
#1 AND #2 AND #3

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4, 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4, 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4, 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4, 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4, 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6, 7, 8, 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6, 7, 8, 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6, 7, 8, 9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6, 7, 8, 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6, 7, 8, 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6, 7, 8, 9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	10
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	10, 11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2, 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2, 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	12

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2: The main characteristics of included studies.

Study	Year	Country	Type of Study	Article Type	NOS Score（0-9）	Jadad Score（0-7）	MINORS Score（0-24）
Virasoro, Ramon et al.	2022	USA, Dominican Republic, Panama	Single-arm Clinical Trial	Journal article	/	/	10
Elliott, S. P. et al.	2022	USA, Canada	RCT	Journal article	/	5	/
Beeder, L. A. et al.	2022	USA	Retrospective Case Study	Journal article	3	/	/
Alibekov, M. M. et al.	2021	Russia	Retrospective Case Study	Journal article	2	/	/
Yi, Y. A. et al.	2020	USA	Retrospective Case Study	Journal article	3	/	/
Kumano, Y. et al.	2019	Japan	Case Control Study	Journal article	5	/	/
Zhou, Y. et al.	2016	China	Retrospective Case Study	Journal article	2	/	/
Yu, S. C. et al.	2016	China	Case Control Study	Journal article	6	/	/
Chhabra, J. S. et al.	2016	India	Retrospective Case Study	Journal article	3	/	/
Ishii, Gen et al.	2015	Japan	Retrospective Case Study	Journal article	3	/	/
Mao, D. et al.	2014	China	Retrospective Case Study	Journal article	2	/	/
Vyas, J. B. et al.	2013	India	Retrospective Case Study	Journal article	3	/	/
Alguersuari, A. et al.	2012	Spain	Retrospective Case Study	Conference abstract	2	/	/
MacDiarmid, S. A. et al.	2000	USA	Retrospective Case Study	Journal article	2	/	/
Mohammed, S. H. et al.	1988	Denmark	Single-arm Clinical Trial	Journal article	/	/	6

NOS, Newcastle Ottawa Scale; MINORS, Methodological Index for Non-randomized Studies.

Supplementary Table 3A. Description and decision criteria for each domain in ROBINS-I

Bias domain	Explanation	Judgments
Bias due to confounding	1. Is there potential for confounding of the effect of intervention in this study? 2. Did the authors use a multivariable-adjusted analysis method that controlled at least for the important confounding domains (age, body mass index, etiology, location of the stricture, length of the stricture, prior intervention management, others) ? 3. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? 4. Did the authors control for any post-intervention variables that could have been affected by the intervention? 5. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? 6. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	1. Low risk of bias: No bias expected due to confounding, including time-varying confounding. 2. Moderate risk of bias: Confounding is expected: including at least 5 factors of the following factors: age, body mass index, etiology, location of the stricture, length of the stricture, prior intervention management, others (i.e. comorbidities, socio-economic status) and have been appropriately controlled for in a multivariable-adjusted analysis. 3. Serious risk of bias: 3-4 above-mentioned factors were measured or appropriately controlled for. 4. Critical risk of bias: less than 3 above-mentioned factors were measured or appropriately controlled for. 5. No information: No information on which confounders have been controlled for.
Bias in selection of participants into the study	1. Was selection of participants into the study based on participant characteristics observed after the start of intervention? 2. Were the post-intervention variables that influenced selection likely to be associated with intervention? 3. Were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? 4. Do start of follow-up and start of intervention coincide for most participants? 5. Were adjustment techniques used that are likely to correct for the presence of selection biases?	1. Low risk of bias: All participants who would have been eligible for the target study were included in the study. 2. Moderate risk of bias: Selection into the study may have been related to exposure and outcome and the authors used appropriate methods to correct for the selection bias. 3. Serious risk of bias: Selection into the study was related to intervention and outcome and this could not be corrected for in the analyses; or the start of follow-up and start of exposure do not coincide and the rate ratio is not constant over time. 4. Critical risk of bias: Selection into the study was very strongly related to intervention and outcome and this could not be corrected for in the analyses; or a substantial amount of follow-up time is likely to be missing from analyses 3.the rate ratio is not constant over time. 5. No information: No information is reported about

		selection of participants into the study.
Bias in classification of interventions	1. Were intervention groups clearly defined? 2. Was the information used to define intervention groups recorded at the start of the intervention? 3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	1. Low risk of bias: The patient clearly underwent urethral balloon dilation, and no measurement error is expected in its assessment. 2. Moderate risk of bias: Intervention status is well defined and some aspects of the assignments of intervention status were determined retrospectively. 3. Serious risk of bias: Intervention status is not well defined; or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome. 4. Critical risk of bias: An extremely high amount of misclassification of intervention status (i.e. because of unusually strong recall biases). 5. No information: No definition of the intervention or no explanation of the source of information about intervention status is reported.
Bias due to deviations from intended interventions	1. Were there deviations from the intended intervention beyond what would be expected in usual practice? 2. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	1. Low risk of bias: Patients did not receive other invasive urethral stricture treatments between the time they underwent balloon dilatation and the follow-up period to assess success. 2. Moderate risk of bias: There were deviations from usual practice, but their impact on the outcome is expected to be slight. 3. Serious or critical risk of bias: There were deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. 4. Critical risk of bias: There were substantial deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. 5. No information: No information on deviations from the intervention is reported.
Bias due to missing data	1. Were outcome data available for all, or nearly all, participants? 2. Were participants excluded due to missing data on intervention status? 3. Were participants excluded due to missing data on other variables needed for the analysis? 4. Are the proportion of participants and reasons for missing data similar across	1. Low risk of bias: Little loss-to-follow-up and data on intervention and other variables were reasonably complete (<10% missing data) and was unlikely to introduce bias; or the analysis addressed missing data and is likely to have removed any risk of bias. 2. Moderate risk of bias: There is a proportion of missing data in the original cohort or a high proportion of loss-to-follow-up; and the analysis is unlikely to have removed the risk of bias arising

	interventions? 5. Is there evidence that results were robust to the presence of missing data?	from the missing data (i.e. using logistic regression). 3. Serious risk of bias: High proportions (>50%) of missing data; and the analysis is unlikely to have removed the risk of bias arising from the missing data; or missing data were addressed inappropriately in the analysis; or the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis. 4. Critical risk of bias: There were critical differences between interventions in participants with missing data; and missing data were not, or could not, be addressed through appropriate analysis. 5. No information: No information is reported about missing data or the potential for data to be missing.
Bias in measurement of outcomes	1. Could the outcome measure have been influenced by knowledge of the intervention received? 2. Were outcome assessors aware of the intervention received by study participants? 3. Were the methods of outcome assessment comparable across intervention groups? 4. Were any systematic errors in measurement of the outcome related to intervention received?	1. Low risk of bias: The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention status of study participants; and any error in measuring the outcome is unrelated to intervention status (i.e., objective measures such as confirmed medical records, record linkage). 2. Moderate risk of bias: The methods of outcome assessment were comparable across intervention groups; and any error in measuring the outcome may be minimally related to intervention status or if the outcome measure was not reliable measured (i.e. confirmed records are not available for the whole study population). 3. Serious risk of bias: The methods of outcome assessment were not comparable across intervention groups; or the outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and error in measuring the outcome was related to intervention status. 4. Critical risk of bias: The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups. 5. No information: No information is reported about the methods of outcome assessment.
Bias in selection of the reported result	1. Is the reported effect estimate likely to be selected from multiple analyses of the intervention-outcome relationship?	1. Low risk of bias: There is a clear description of all analyses and the analyses are consistent and all reported results correspond to all intended outcomes,

	2. Is the reported effect estimate likely to be selected from different subgroups?	analyses and sub-cohorts. 2. Moderate risk of bias: The analyses are clearly defined; and there is an indication of selection of the reported analysis from among multiple analyses; and there is an indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results (i.e. estimates not shown for all analyses). 3. Serious risk of bias: There is a high risk of selective reporting from among multiple analyses; or the cohort or subgroup is selected from a larger study for analysis and appears to be reported based on the results. 4. Critical risk of bias: There is evidence or strong suspicion of selective reporting of results; and the unreported results are likely to be substantially different from the reported results. 5. No information: There is too little information to make a judgment.

Overall judgment

1. Low risk of bias

The study is judged to be at a low risk of bias for all domains.

2. Moderate risk of bias

The study is judged to be at low or moderate risk of bias for all domains.

3. Serious risk of bias

The study is judged to be at serious risk of bias in at least one domain, but not at critical risk in any domain.

4. Critical risk of bias

The study is judged to be at critical risk of bias in at least one domain.

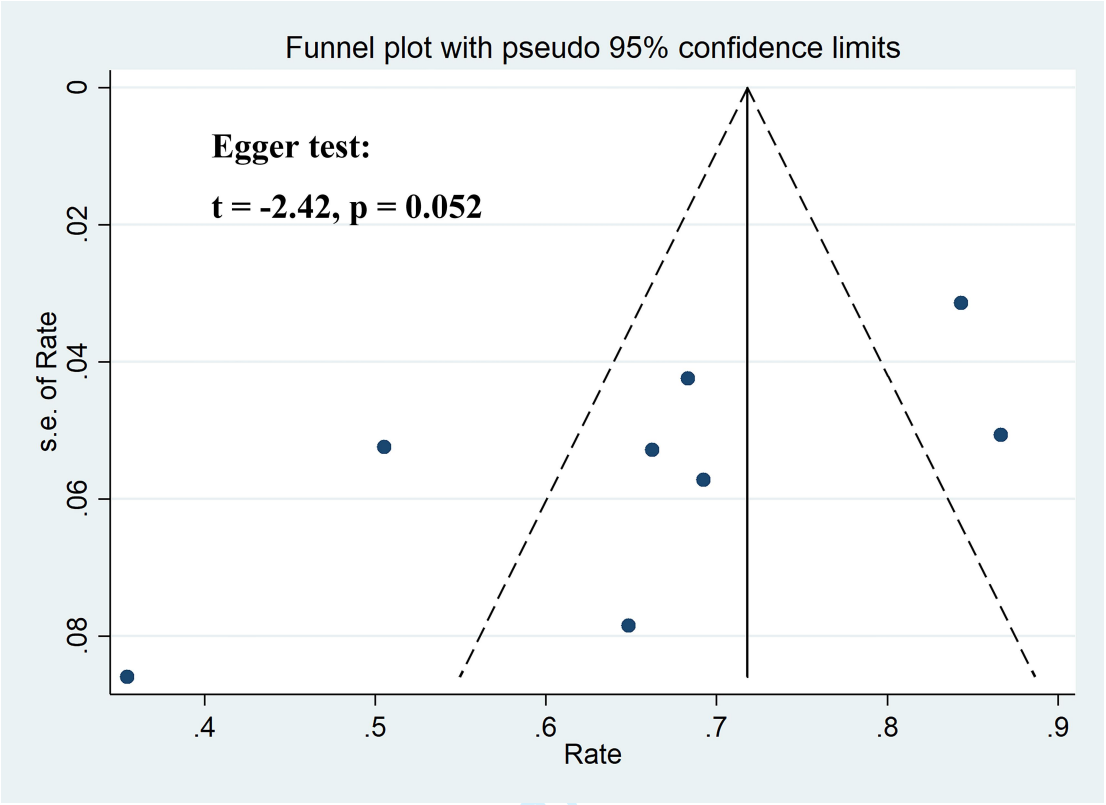
Supplementary Table 3B. Quality assessment results using the ROBINS-I tool

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall judgment
Virasoro, Ramon et al. 2022	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Beeder, L. A. et al. 2022	Moderate	Serious	Moderate	Low	Low	Serious	Moderate	Serious
Alibekov, M. M. et al. 2022	Serious	Serious	Moderate	Low	Low	Serious	Serious	Serious
Yi, Y. A. et al. 2020	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Kumano, Y. et al. 2019	Serious	Serious	Moderate	Low	Low	Serious	Moderate	Serious
Zhou, Y. et al. 2016	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Yu, S. C. et al. 2016	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Chhabra, J. S. et al. 2016	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Ishii, Gen et al. 2015	Serious	Critical	Moderate	Low	Low	Serious	Moderate	Critical
Mao, D. et al. 2014	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Vyas, J. B. et al. 2013	Serious	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Alguersuari, A. et al. 2012	Serious	Serious	Moderate	Low	Low	Serious	Serious	Serious
MacDiarmid, S. A. et al. 2000	Serious	Serious	Moderate	Low	Moderate	Serious	Moderate	Serious
Mohammed, S. H. et al. 1988	Critical	Serious	Low	Low	Moderate	Serious	Serious	Critical

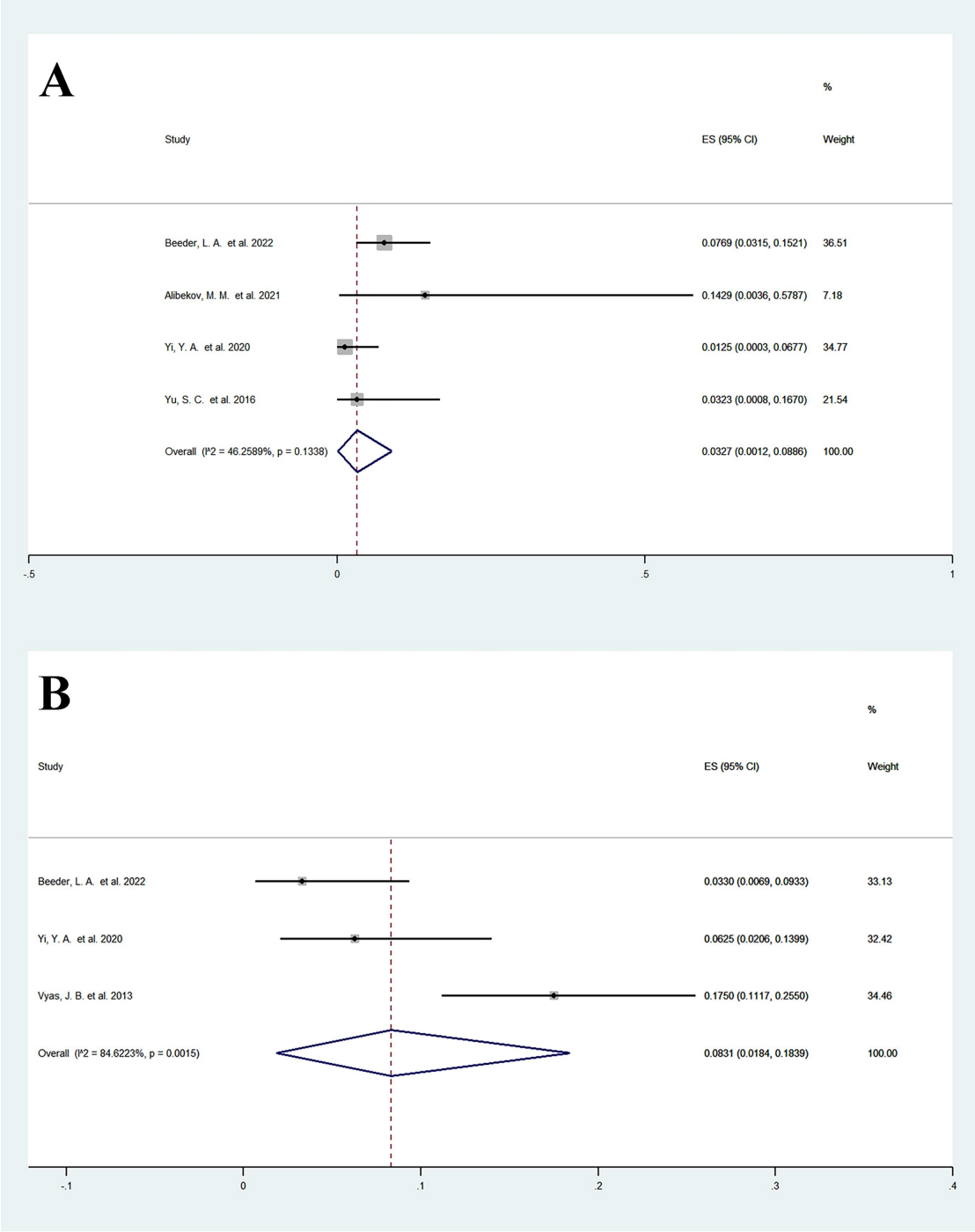
Supplementary Table 4: Sensitivity analysis of the pooled results of conventional balloon dilation success rate.

Excluded Study	Pooled Results (%)	95% Confidence Interval	
Beeder, L. A. et al. 2022	69.57	58.61	79.55
Yi, Y. A. et al. 2020	67.12	54.10	78.96
Zhou, Y. et al. 2016	64.13	52.45	75.03
Yu, S. C. et al. 2016	70.64	60.47	79.90
Chhabra, J. S. et al. 2016	64.05	53.49	73.99
Mao, D. et al. 2014	67.31	54.95	78.59
Vyas, J. B. et al. 2013	66.76	53.20	79.09
Alguersuari, A. et al. 2012	66.69	53.81	78.45

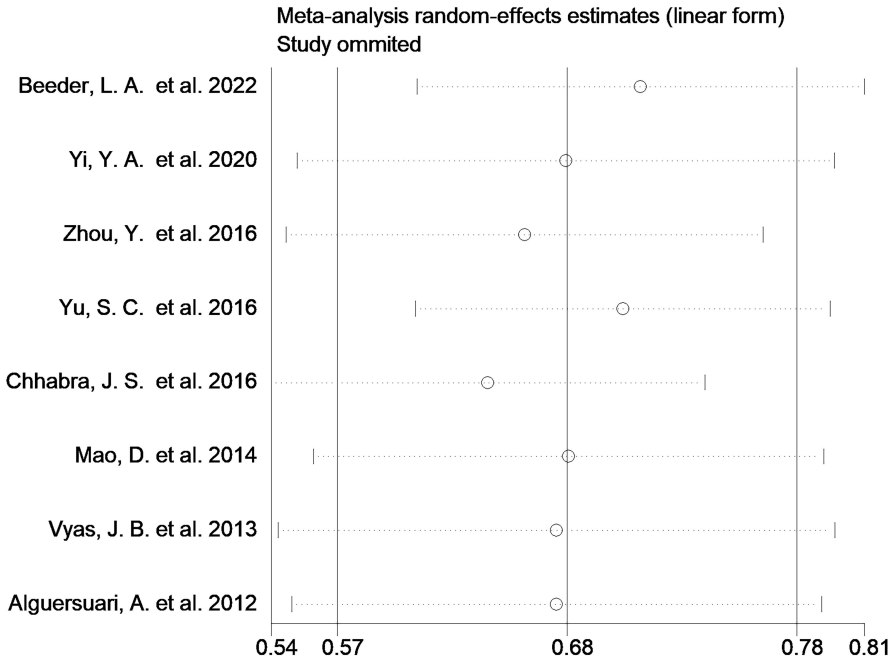
Supplementary Figure 1: The funnel plot of conventional balloon dilation success rate.



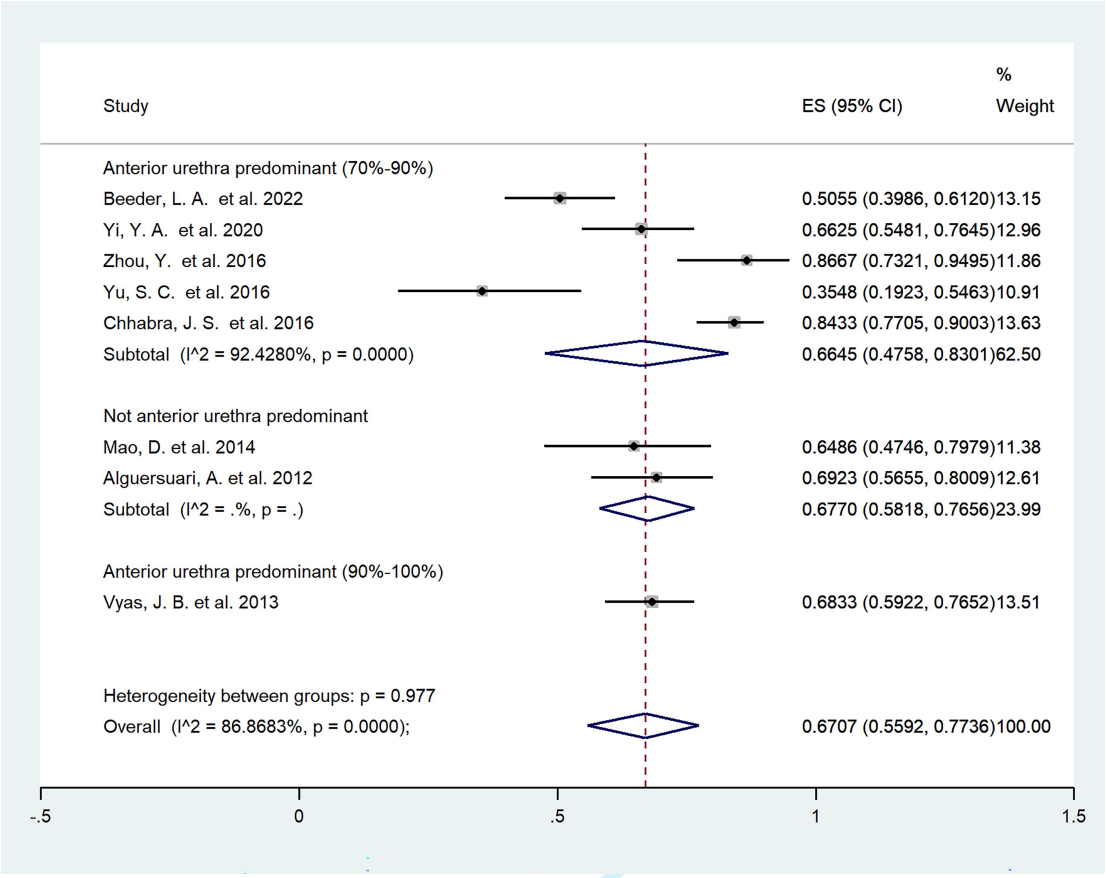
Supplementary Figure 2: Forest plots showing the safety of balloon dilation. (A) Incidence of infection; (B) Incidence of urinary retention. CI, confidence interval.



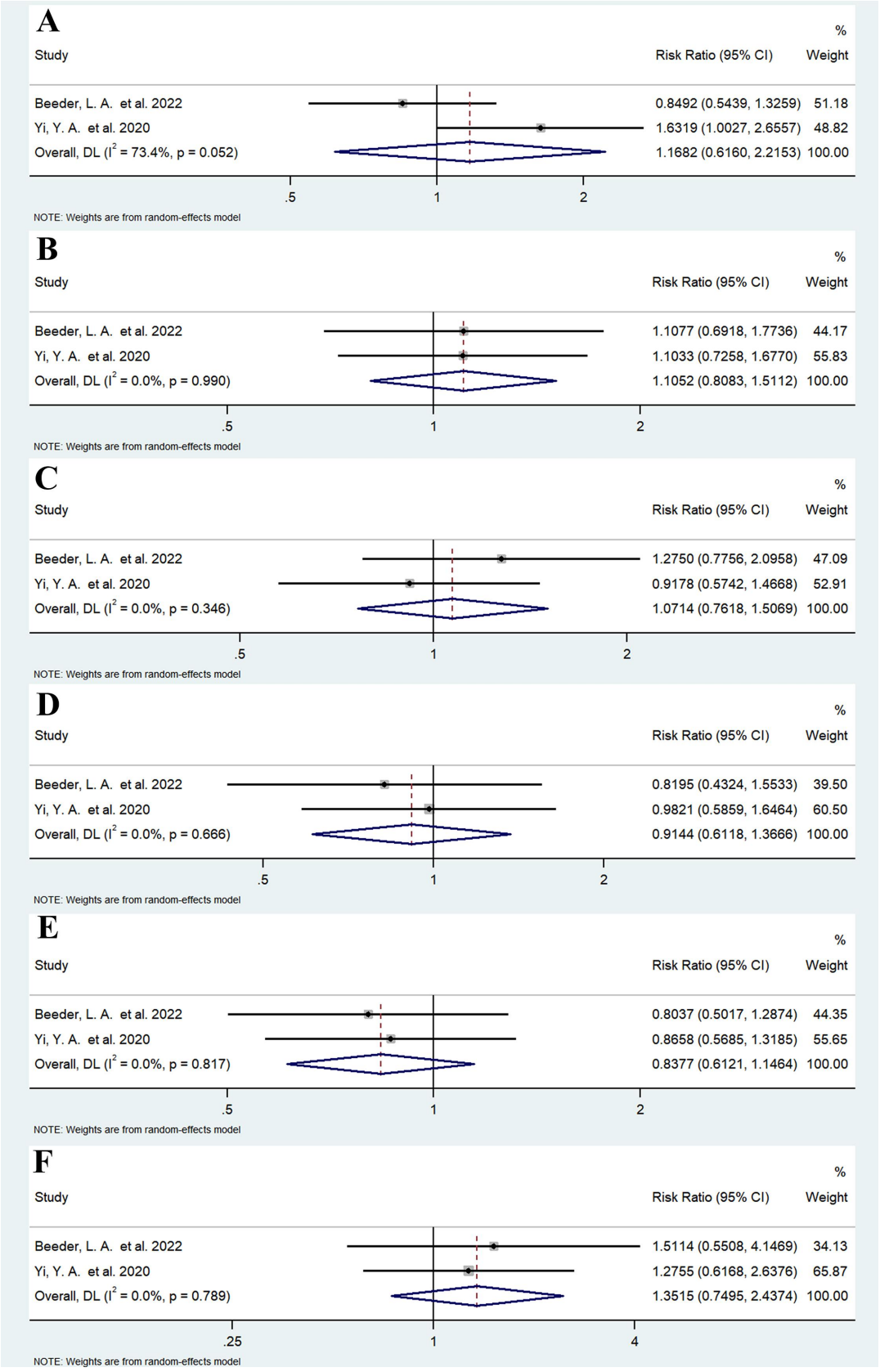
Supplementary Figure 3: The sensitivity analysis of conventional balloon dilation success rate.



Supplementary Figure 4: Forest plots showing the subgroup analysis of conventional balloon dilation success rate according to the percentage of anterior urethral strictures.



Supplementary Figure 5: Forest plots showing other possible influencing factors of balloon dilation. (A) with and without previous urethroplasty; (B) History of smoking; (C) Coronary heart disease; (D) Diabetes mellitus; (E) Hypertension; (F) Chronic obstructive pulmonary disease. CI, confidence interval.



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Balloon dilation for the treatment of male urethral strictures: A Systematic Review and Meta-analysis

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Abstract

Objective: The use of minimally invasive endoluminal treatment for urethral strictures has been a subject for debate for several decades. The aim of this study was to review and discuss the safety, efficacy and factors influencing the clinical application of balloon dilation for the treatment of male urethral strictures.

Design: Systematic review and meta-analysis.

PROSPERO registration number: CRD42022334403.

Data sources: Embase, Medline, Web of Science, Cochrane Library and Scopus were searched for publications published before July 17, 2022.

Study selection: Two independent researchers screened and assessed the results, and all clinical studies on balloon dilation for the treatment of urethral strictures in men were included.

Data extraction and synthesis: The success rate, rate of adverse events, International Prostate Symptom Scores (IPSS), maximum uroflow (Qmax) and postvoid residual urine volume (PVR) were the main outcomes. Stata 14.0 was used for statistical analysis.

Results: Fifteen studies with 715 patients were ultimately included in this systematic review. The pooled results of eight studies showed that the reported success rate of simple balloon dilation for male urethral strictures was 67.07% (95% CI: 55.92%-77.36%). The maximum urinary flow rate at 3 months (RR=2.6510, 95% CI: 1.0681-4.2338, $p < 0.01$) and the maximum urinary flow rate at one year (RR=1.6637, 95% CI: 1.1837-2.1437, $p < 0.05$) were significantly different after dilation. There is insufficient evidence to suggest that balloon dilation is superior to optical internal urethrotomy (OIU) or direct visual internal urethrotomy (DVIU) (RR=1.4754, 95% CI: 0.7306-2.9793, p=0.278).

Conclusion: Balloon dilation may be an intermediate step before urethroplasty and is a promising alternative therapy to simple dilation and DVIU. The balloon is a promising drug delivery tool, and paclitaxel drug-coated balloon dilation is effective in reducing retreatment rates in patients with recurrent anterior urethral strictures. The etiology, location, length, previous treatment of urethral stricture may be associated with the efficacy of balloon dilation.

Key words: Balloon dilation, urethral stricture, systematic review, meta-analysis

Strengths and limitations of this study

- This study systematically reviewed the principle, safety, and efficacy of balloon dilatation and described intermittent urethral balloon self-dilation.
- We provide a comprehensive analysis of factors such as etiology, stricture location, stricture length, and prior management intervention and discuss the clinical directions for balloon dilation.
- The quality of the included studies was relatively low, and there was a considerable risk of bias.
- Most of the included studies were retrospective observational studies that lacked valid controls, and the results need to be interpreted with caution.

1. Introduction

Urethral stricture is relatively common disease in men and is described as any abnormal narrowing of the anterior or posterior urethra. In some susceptible populations, the incidence of male urethral stricture disease is as high as 0.6%, with more than 5,000 individuals hospitalized per year [1]. The most common symptoms in patients are weakened urine flow and even urinary retention, which seriously affects the quality of life [2]. The etiology of urethral stricture is complex, is complex and includes trauma, infection, iatrogenic, lichen sclerosus, idiopathic, etc. Iatrogenic urethral injury is the most common type of urethral stricture in resource-rich countries, whereas urethral injuries caused by infection and trauma are more common in developing countries [3, 4]. With continuous developments in medical technology, the rapid increase in the incidence of iatrogenic urethral stricture warrants further investigation. Catheterization, transurethral manipulation, prostate surgery, radiotherapy, and chemotherapy can cause irreversible stricture of the urethra [5-8].

Although urethroplasty has been recognized as a curative treatment for urethral strictures, dilation and direct visual internal urethrotomy (DVIU) are still widely used and effective for single bulbar urethral strictures < 2 cm, for which the success rate is 35-70% [3, 9]. There is currently a lack of evidence evaluating whether dilation or DVIU is more effective than the other methods, so both have the same therapeutic indications [10].

Balloon dilation is a special type of dilation that has a long history of treating urethral strictures in men. Russinovich, N. A. E. et al. were first to report the outcomes of balloon dilation performed in 7 males with urethral stricture in 1980; this type of dilation was painless compared to traditional dilation methods and was not prone to cause mucosal or periurethral injury [11]. Subsequently, Pinot, J. J. dilated the urethra of 25 patients using an inflatable balloon catheter, which included atraumatic catheterization through a vascular catheter under urethroscopy, followed by inflation of the balloon catheter into a flexible guidewire [12]. Dilation was controlled under the guidance of voiding urethrography and was much less uncomfortable than conventional urethral dilation; only 3 of 25 patients needed to undergo a repeat procedure. Immediately, Glesy, J. D. designed a new coaxial balloon dilator for the treatment of urethral stricture and noted that the balloon dilator can expand slowly and gradually, which is better than traditional rapid and sudden expansion [13]. Several studies have shown that balloon dilation results in minimal trauma and immediate symptom relief, with less patient discomfort and a lower complication rate [14-19]. Since there is some radiation exposure with angiography, B-ultrasound has been used to facilitate control of balloon dilation, and good clinical results have been initially achieved [20]. Further research revealed that balloon dilation under the guidance of cystoscopy gently, safely and effectively dilates the urethra [21].

Although balloon dilation is a well-tolerated minimally invasive endoluminal surgical procedure widely used in practice, its clinical significance has not been systematically and comprehensively reviewed. Our objective was to assess the efficacy, safety and factors influencing the clinical application of balloon dilation.

2. Materials and methods

2.1 Search strategy

Reporting in this study was in accordance with the guidelines of the PRISMA statement [22] (Supplementary Table 1), and the specific protocol was registered on PROSPERO with the registration number CRD42022334403. Using Medical Subject Headings and free text terms, we searched for relevant articles published prior to July 17, 2022, in the following databases: Medline, Embase, Cochrane Library, Web of Science and Scopus. The search strategy is shown in the Supplementary File.

2.2 Eligibility criteria

Two researchers (X.L. and C.X.) screened and assessed the search results independently. The inclusion criteria were as follows: (1) studies with male patients diagnosed with urethral strictures; (2) studies in which balloon dilation was applied as the main intervention, not including patient self-dilation; (3) clinical studies, retrospective or prospective; (4) studies reporting the success and adverse event rates. Conference abstracts were eligible for inclusion if they reported sufficient outcome data. If several articles were all related to the same study, the most recent publication with the most complete data was included in the systematic review. A consensus was finally reached through consultation and discussion in the event of any disagreements or differences between the two researchers.

2.3 Quality assessment

The quality of the included studies was independently assessed by two researchers (X.L. and C.X.). All observational studies were assessed using the Newcastle–Ottawa Scale (NOS) in terms of population selection, comparability, and outcome evaluation [23]. Randomized controlled trials (RCTs) were assessed using the Jadad Quality Scale, and articles with a score >3 were considered high-quality research [24]. For single-arm clinical trials, the first 8 items of the Methodological Index for Non-randomized Studies (MINORS) scale were used for assessment[25]. The ROBINS-I tool was used to further assess the risk of bias in non-randomized controlled trials [26].

2.4 Data extraction

We extracted data on the success rate, adverse event rate, International Prostate Symptom Score (IPSS), maximum uroflow (Qmax, mL/sec) and postvoid residual urine volume (PVR). When disagreements arose, a third reviewer participated in the discussions and mediated to reach a consensus.

2.5 Statistical analysis

Stata 14.0 (StataCorp, USA) was used for statistical analysis, and the success and adverse event rates were reported as proportions. The I^2 index was used to test for between-study heterogeneity. An $I^2 > 50\%$ was considered to indicate significant

heterogeneity, and the random effects model was used for pooled analysis; otherwise, less heterogeneity was considered, and the fixed effects model was used. By excluding each study one by one, we performed a sensitivity analysis of the balloon dilation success rate to assess the stability and reliability of the pooled results. Subgroup analyses were performed according to the results of the meta-regression models.

2.6 Patient and public involvement

None.

3. Results

3.1 Study selection

The flowchart of the study retrieval process is shown in Figure 1. Fifteen studies were included in the systematic review, involving a total of 842 patients. Table 1 and Table 2 present the main characteristics of the included studies. Among these, there were 1 randomized controlled trial (RCT) [27], 2 single-arm clinical trials [28, 29], 2 case–control studies [30, 31], and 10 retrospective case studies [32-41].

3.2 Quality analysis and risk of bias

We evaluated the quality of the 15 studies included in the systematic review, and the results are presented in Supplementary Table 2. Most of the current studies in this article are retrospective, with inadequate study designs and a lack of valid controls.

We further conducted a bias analysis of 14 non-randomized controlled trials using the ROBINS-I tool, and the evaluation criteria and results are shown in Supplementary Table 3. Since the operation is often influenced by the subjective preferences of the surgeons and most of the included studies are retrospective case studies, unavoidable selection bias is one of the most prominent issues. Selection bias is exacerbated in some small-sample studies of patients with specific comorbid conditions, such as coexisting urinary calculi. Some confounding factors such as age, body mass index, etiology of the stricture, location of the stricture, length of the stricture, prior management, and other factors, such as patient baseline physical condition, were present in most studies. Some of these confounding factors were not appropriately controlled for in the multivariable adjusted analysis. Some outcome measures of balloon dilation are subjective, and researchers may also exaggerate the efficacy of the procedure to publicize its advantages. Moreover, a funnel plot of eight studies included in the evaluation of the conventional balloon dilation success rate was generated, and there was no evidence of publication bias (Egger test: $t=-2.42$, $p=0.052>0.05$) (Supplementary Figure 1). In addition, due to the small sample sizes of some of the included studies, there are some limitations in reflecting the overall clinical situation.

3.3 The principle of balloon dilation

The principle of balloon dilation is to apply radial force along the balloon span at the

stricture site. While the principle of traditional optical internal urethrotomy is to achieve epithelial regeneration by incising scar tissue. Compared with the parallel force applied by simple dilation, balloon dilation applies less shear force and causes less trauma, which can reduce the risk of cavernous fibrosis development and cause less discomfort [31, 42, 43]. Balloon dilation can also cause the fibrous scar in the stricture to more evenly fracture, resulting in 360° annular expansion, thereby increasing the inner diameter of the stenotic segment; during the balloon dilation process, the urethral pressure gradually increases, and the balloon is slowly and gently expanded to minimize damage to blood vessels and urethral tissue [13]. Balloon dilation tends to achieve extrusion molding in a single pass, and the high pressure of the balloon is effective in compressing the bleeding point. In addition, the smooth surface of balloon can prevent normal urethral mucosal damage.

3.4 Safety assessment and incidence of adverse events

Urinary tract infection, urinary retention, postoperative haematuria and dysuria are the main complications of balloon dilation. Therefore, strict aseptic and standardized operations are needed during surgery to prevent and avoid the occurrence of adverse events as much as possible.

We performed a pooled analysis of reported adverse event rates for urinary tract infection and urinary retention. The pooled incidence of infection in patients after balloon dilation was 3.27% (95% CI: 1.2%-8.86%; heterogeneity: I^2=46.2589%, p= 0.1338) (Supplementary Figure 2A). However, the pooled incidence of urinary retention was 8.31% (95% CI: 1.84%-18.39%; heterogeneity: I^2=84.6223%, p<0.05) (Supplementary Figure 2B). Urinary tract infection is the most common complication within 30 days of balloon dilation, and some patients require antibiotic treatment [32]. Some patients also have transient haematuria after surgery, but no further treatment, such as blood transfusion, is needed [31, 32]. Furthermore, Yu, S. C. 's study also revealed that the incidence of major postoperative complications, such as urethral bleeding and urinary tract infection, in the balloon dilation group was lower than that in the DVIU group (urethral bleeding: 2/31 vs. 8/25, P=0.017; UTI: 1/31 vs. 6/25 P=0.037) [31].

3.5 Clinical efficacy of balloon dilation for male urethral strictures

3.5.1 Conventional balloon dilation success rate

For studies with conventional balloon dilation, we defined success of balloon dilation as no recurrence or no further stricture treatment during the follow-up period, excluding studies with a sample size of less than 30 on account of the potentially greater selection bias and merging data from 8 studies published in 2012-2022 [31, 32, 34-36, 38-40]. Reported success rates varied from 35.5% to 86.7%. The pooled balloon dilation success rate was 67.07% (95% CI: 55.92%-77.36%; heterogeneity: I^2=86.8683%, p<0.05) (Figure 2A). Six of these studies reported follow-up, with a median pooled follow-up time of 13.50 months (95% CI: 12.86-14.14%; heterogeneity: I^2=99.2%, P<0.05). This result needs to be interpreted with caution and most likely overestimates the efficacy of balloon dilation. Clinical data obtained

during long-term follow-up are lacking, and the real-world balloon dilation success rate should decline progressively with longer follow-up. Moreover, the assessment of the success rate of balloon dilation involves significant subjective factors that may exaggerate efficacy.

We performed a sensitivity analysis by excluding studies one by one. The recalculated results are shown in Supplementary Table 4 and Supplementary Figure 3. Compared to the pooled results of all the studies, the maximum deviation rate was 5.3%, indicating that the final pooled result was relatively stable. We performed a meta-regression analysis and found that factors such as the location of the stricture ($t=5.25$, $p<0.05$), length of the stricture ($t=7.97$, $p<0.05$), and age ($t=7.97$, $p<0.05$) may be associated with high heterogeneity, and subgroup analyses of these factors were performed as described in Section 3.6.

3.5.2 Drug coated balloon dilation success rate

Balloons coated with drugs such as paclitaxel have achieved promising clinical results in recent years. Two studies on paclitaxel-coated balloons for recurrent urethral strictures revealed the considerable effect of these devices on recurrent urethral strictures, with a relatively objective functional success rate (67%) and an anatomical success rate (74.6%) [27, 28]. The functional success rate was defined as the percentage of subjects with ≥50% improvement in IPSS scores who did not require retreatment. The anatomical success rate was defined as the proportion of participants for whom a 16Fr flexible cystoscope or a 14Fr catheter could atraumatically pass through the treated area at 6 months postoperatively. Both drug balloon studies were performed in patients with recurrent anterior urethral strictures who had received at least 1 prior endoscopic treatment. The patients had urethral strictures ⩽12F, all less than 3 cm in length. The IPSS scores were greater than 11, and all the patients had urinary flow rates of at least 15 ml/s or less. These studies excluded patients with prior urethroplasty, lichen sclerosus, neurogenic bladder, bladder neck contracture, artificial urinary sphincter, or other confounding etiologies.

3.5.3 Assessment of patient's clinical symptoms

The changes in the urinary flow rate, PVR, and IPSS are summarized in Table 3. Compared with that preoperatively, the postoperative maximum urinary flow rate was greatly improved at 3 months (RR=2.6510, 95% CI: 1.0681-4.2338; $z=3.282$, $p < 0.01$; $I^2=96.5\%$, $p < 0.05$), and the significant difference remained at one year postoperatively (RR=1.6637, 95% CI: 1.1837-2.1437; $z=6.794$, $p < 0.01$; $I^2=78.8\%$, $p < 0.05$). The patient's IPSS scores and PVR also decreased accordingly.

Patients' subjective perception of improvement in voiding symptoms is a crucial indicator of the true efficacy of urethral stricture treatment, and the results are summarized in Table 4. The ROBUST III study [28] revealed that patients' International Prostate Symptom Score-Quality of Life (IPSS QoL) scores increased significantly by 30 days after balloon dilation, indicating outstanding short-term efficacy. Moreover, three-year follow-up results from the ROBUST I trial study [27] indicated significant improvements in both QoL scores and Patient-Reported

Outcome Measure for Urethral Stricture Surgery (USS-PROM) scores for patients who underwent balloon dilation compared to baseline status ($p<0.0001$). With the extension of follow-up time, the quality of life of the patients remained good, reflecting the long-term effectiveness of balloon dilation.

Table 1: Clinical characteristics and efficiency of balloon dilation (I).

Study	Evaluable Patients (n)	Age (average)	Etiology	Location of the Strictures	Length of Stricture	Predilated state
Virasoro, Ramon et al.	43	50.7 (22.0-81.0)	/	Anterior urethra	≤ 2 cm	1–4 prior endoscopic treatments (none within 3 months of enrolment)
Elliott, S. P. et al.	60 (79): 15 (48)*	60.6 ± 16.0 : 58.7 ± 15.5	Iatrogenic (21/78, 26.9%); Idiopathic (42/78, 53.8%); Inflammatory (1/78, 1.3%); Traumatic (14/78, 17.9%); pelvic radiation (9/79, 11.4%)	Anterior urethra	≤ 3 cm	≥ 2 prior endoscopic treatments
Beeder, L. A. et al.	91	61	/	Anterior urethra (n=75, 82%); posterior urethra (n=16, 18%)	/	Most (75/91, 82%) had prior treatment for USD (endoscopic 50/91 (55%), 51/91 (56%) urethroplasty)
Alibekov, M. M. et al.	7	52 (47-65)	Idiopathic (4/7, 57.1%); Inflammatory (1/7, 14.3%); Traumatic (2/7, 28.6%)	Anterior urethra	≤ 1 cm	All patients had 1 urethral stone. The sizes of the stone ranged from 4 to 9 mm (median - 6 mm)
Yi, Y. A. et al.	80	/	/	Anterior urethra (n=59, 74%); posterior urethra (n=21, 26%)	≤ 1.5 cm	Over 75% of patients had some form of prior stricture treatment, including dilation (34/80, 42.5%), DVIU (19/80, 23.8%), or urethroplasty (48/80, 60%)
Kumano, Y. et al.	13 : 9	71 : 63	Iatrogenic (10/13, 76.9%); Idiopathic (3/13, 23.1%)	Anterior urethra (n=9, 41%); posterior urethra (n=13, 59%)	/	/
Zhou, Y. et al.	45	46.6 (22-76)	Iatrogenic (19/45, 42.2%); Inflammatory (5/45, 11.1%); Traumatic (18/45, 40%); pelvic radiation (3/45, 6.7%)	Anterior urethra (n=36, 80%); posterior urethra (n=9, 20%)	≤ 2 cm	5 patients had a prior suprapubic cystostomy
Yu, S. C. et al.	31 : 25	49 (32-67) : 44 (24-71)	Iatrogenic (7/31, 22.6%); Idiopathic (1/31, 3.2%); Inflammatory (2/31, 6.5%); Traumatic (21/31, 67.7%);	Anterior urethra (n=45, 80%); posterior urethra (n=11, 20%)	≤ 1 cm (n=48, 86%) ; > 1 cm (n=8, 14%)	None received prior endovascular therapy

Chhabra, J. S. et al.	134 (144)*	52 (18-85)	Iatrogenic (59/144, 41.0%); Idiopathic (84/144, 58.3%); pelvic radiation (1/144, 0.7%)	Anterior urethra (n=110, 76%); posterior urethra (n=8, 6%); both (n=26, 18%)	≤ 1.5 cm (n=130, 90%) ; > 1 cm (n=14, 10%)	/
Ishii, Gen et al.	10	70 (61-75)	Iatrogenic	Posterior urethra	/	All patients had cystourethral anastomotic stricture after radical prostatectomy
Mao, D. et al.	37 (39)*	55 (24-84)	/	Anterior urethra (n=17, 44%); posterior urethra (n=20, 51%); both (n=2, 5%)	≤ 2 cm	/
Vyas, J. B. et al.	120	49.86 (30-85)	/	Anterior urethra (n=114, 95%); posterior urethra (n=6, 5%)	≤ 1.5 cm	/
Alguersuari, A. et al.	65	63.17 ± 16.9	/	Anterior urethra (26.2%); posterior urethra (73.8%)	≤ 2 cm (86.2%) ; > 2 cm (13.8%)	/
MacDiarmid, S. A. et al.	51	/	Iatrogenic (27/51, 52.9%); Idiopathic (11/51, 21.6%); Inflammatory (10/51, 19.6%); Traumatic (3/51, 5.9%)	Anterior urethra (n=49, 96%); posterior urethra (n=2, 4%)	/	/
Mohammed, S. H. et al.	6 (7)*	35 (16-67)	Iatrogenic (1/6, 16.7%); Idiopathic (2/6, 33.3%); Inflammatory (2/6, 33.3%); Traumatic (1/6, 16.7%)	Anterior urethra (n=4, 57%); posterior urethra (n=3, 43%)	/	/

* the number of people who were initially assessed at baseline in the study is in parentheses, and the number of people who could be effectively assessed at the end of the follow-up is outside the brackets.

Table 2: Clinical characteristics and efficiency of balloon dilation (Ⅱ).

Study	Balloon Types	Control	Definition of Success Rate	Reported Success Rate (%)	Follow-up
Virasoro, Ramon et al.	Optilume® drug coated balloon (DCB)	/	Functional success was defined as ≥50% reduction in International Prostate Symptom Score (IPSS) without need for retreatment.	67	3 years
Elliott, S. P. et al.	Optilume® drug coated balloon (DCB)	dilation/DVIU	Anatomical success: the proportion of participants in whom the surgeons could atraumatically pass a 16-French flexible cystoscope or a 14-French catheter through the treated area at 6 months	74.6 : 26.8	1 year

Beeder, L. A. et al.	8-cm, 24-French UroMax Ultra™ balloon dilator	/	Proportion of patients who reported no recurrence of lower urinary tract symptoms or did not need further stricture treatment	50	12 months (3-40)
Alibekov, M. M. et al.	/	/	Proportion of patients without recurrence of urethral stricture 18 months of dilation	85.7	14 months (3-24)
Yi, Y. A. et al.	8-cm, 24-French UroMax Ultra™ balloon dilator	/	Proportion of patients with no postoperative recurrence of urethral stricture or who did not need further stricture treatment	66.3	8.4 months (IQR, 3.9-22)
Kumano, Y. et al.	Balloon dilation catheter (X-FORCE; BARD Medical, Murray Hill, NJ, USA)	OIU	Proportion of patients with no recurrence of stricture during the follow-up period	84 : 22	/
Zhou, Y. et al.	Balloon catheter (X-Force™, C.R. Bard Inc., USA)	/	Proportion of patients who did not need further stricture treatment during the follow-up period	86.7	6-24 months
Yu, S. C. et al.	6-cm, 7-French balloon catheter (X-Force™, C.R. Bard Inc., USA)	DVIU	Proportion of patients with no postoperative recurrent urethral stricture or who did not need further stricture treatment	35.5	14.75 months (5-36)
Chhabra, J. S. et al.	8-cm, 24-French urethral Balloon catheter set (Cook Urological, Spencer, Ind., USA)	/	Proportion of patients who did not need further stricture treatment during the follow-up period	84.4	24 months (3-52)
Ishii, Gen et al.	6-cm, 6-French Balloon catheter, the X Force®	/	Proportion of patients with no recurrence of strictureduring the follow-up period	80	24 months (7-67)
Mao, D. et al.	24-French Nephrostomy balloon dilation catheter, the X Force®	/	Proportion of patients who did not need further stricture treatment during the follow-up period	64.9	/
Vyas, J. B. et al.	8-cm, 24-French urethral Balloon catheter set (Cook Urological, Spencer, Ind., USA)	/	Proportion of patients who did not need further stricture treatment during the follow-up period	68	6 months (2-60)
Alguersuari, A. et al.	fluoroscopic- guided balloon dilation	/	Proportion of patients who did not need further stricture treatment during the follow-up period	69	/
MacDiarmid, S. A. et al.	The UrethraMax (4, 6, or 8-cm; 24-French) or a coude tip balloon dilation catheter	/	Proportion of patients who did not need further stricture treatment during the follow-up period	55	9 months (1-16)
Mohammed, S. H. et al.	Olbert balloon catheter	/	Proportion of patients who did not need further stricture treatment during the follow-up period	66.7	12 months (6-26)

DVIU, direct vision internal urethrotomy; OIU, optical internal urethrotomy.

Table 3: Changes in the urinary flow rate, PVR, and IPSS after balloon dilation. (The following table is continued to the right)

Study	Location of the Strictures	Length of Strictures
Virasoro, Ramon et al. 2022	Anterior urethra	≤ 2 cm
Elliott, S. P. et al. 2022	Anterior urethra	≤ 3 cm
Zhou, Y. et al. 2016	Anterior urethra (n=36, 80%); posterior urethra (n=9, 20%)	≤ 2 cm
Chhabra, J. S. et al. 2016	Anterior urethra (n=110, 76%); posterior urethra (n=8, 6%); both (n=26, 18%)	≤ 1.5 cm (n=130, 90%); > 1 cm (n=14, 10%)
Vyas, J. B. et al. 2013	Anterior urethra (n=114, 95%); posterior urethra (n=6, 5%)	≤ 1.5 cm
MacDiarmid, S. A. et al. 2000	Anterior urethra (n=49, 96%); posterior urethra (n=2, 4%)	/

IPSS					
Before surgery	**3 months**	**6 months**	**1 year**	**2 years**	**3 years**
25.2 ± 4.5 （n=53)	6.1 ± 7.6 (n=51)	4.6 ± 5.2 (n=45)	4.5 ± 3.9 (n=40)	6.9 ± 7.7 (n=38)	5.5 ± 6.9 (n=33)
22.0 ± 6.8 （n=79)	7.4 ± 5.8 (n=74)	8.3 ± 6.2 (n=71)	9.0 ± 7.1 (n=67)	/	/
/	/	/	/	/	/
/	/	12.7 (n=112)	12.6 (n=112)	/	/
21.6 (n=120)	11.4 (n=120)	12.6 (n=120)	/	/	/
/	/	/	/	/	/
Qmax (mL/sec)					
Before surgery	**3 months**	**6 months**	**1 year**	**2 years**	**3 years**
5.0 ± 2.6 (n=46)	22.2 ± 12.5 (n=51)	19.8 ± 10.8 (n=45)	20.1 ± 10.0 (n=39)	17.5 ± 10.4 (n=38)	15.1 ± 8.3 (n=33)
7.6 ± 3.4 (n=78)	18.6 ± 10.9 (n=71)	16.6 ± 8.9 (n=69)	15.5 ± 9.0 (n=65)	/	/

5.6 ± 1.4 (n=45)	19.8 ± 3.9 (n=45)	/	/	/	/
5.2 ± 2.7 (n=144)	/	15.4 ± 7.2 (n=112)	12.6 ± 5.7 (n=112)	/	/
5.7 (n=120)	14.3 (n=120)	12.7 (n=120)	/	/	/
10.4 (n=48)	15.3 (n=43)	17.7 (n=27)	15.2 (n=5)	/	/

PVR (mL)					
Before surgery	**3 months**	**6 months**	**1 year**	**2 years**	**3 years**
141.4 ± 105.1 (n=43)	141.4 ± 105.1 (n=51)	30.0 ± 42.8 (n=45)	24.6 ± 32.1 (n=39)	45.5 ± 49.5 (n=38)	50.2 ± 62.5 (n=33)
109.8 ± 116.9 (n=77)	103.4 ± 134.4 (n=70)	73.1 ± 117.7 (n=67)	94.6 ± 121.8 (n=66)	/	/
/	/	/	/	/	/
/	/	/	/	/	/
90.2 (n=120)	34.2 (n=120)	20.2 (n=120)	/	/	/
/	/	/	/	/	/

IPSS, International Prostate Symptom Scores; Qmax, maximum uroflow; PVR, postvoid residual urine volume.

Table 4: Changes in the USS-PROM score, IPSS-QOL, and IIEF score after balloon dilation.

Study: Virasoro, Ramon et al. 2022						
Scoring items	**Before surgery**	**3 months**	**6 months**	**1 year**	**2 years**	**3 years**
USS-PROM	15.9 ± 4.7 (n=53)	3.2 ± 5.5 (n=51)	1.9 ± 2.9 (n=45)	1.4 ± 1.8 (n=40)	3.6 ± 5.8 (n=38)	2.0 ± 3.5 (n=33)
IPSS QoL	4.9 ± 0.9 (n=53)	0.8 ± 1.3 (n=51)	0.7 ± 0.9 (n=45)	0.7 ± 0.9 (n=40)	0.9 ± 1.5 (n=38)	0.7 ± 1.2 (n=33)
IIEF - OS	6.5 ± 2.6 (n=53)	7.9 ± 2.5 (n=51)	7.9 ± 2.5 (n=45)	8.1 ± 2.5 (n=40)	7.6 ± 2.5 (n=38)	8.2 ± 2.2 (n=33)
IIEF - EF	16.0 ± 12.2 (n=53)	20.7 ± 12.0 (n=51)	21.0 ± 11.8	22.1 ± 10.9	21.1 ± 11.9	22.5 ± 11.2 (n=33)

			(n=45)	(n=40)	(n=38)	
Study: Elliott, S. P. et al. 2022						
Scoring items	**Before surgery**	**30 days**	**3 months**	**6 months**	**1 year**	/
IPSS QoL	4.5 ± 1.3 (n=79)	1.7 ± 1.4 (n=78)	1.6 ± 1.4 (n=74)	1.7 ± 1.3 (n=71)	1.9 ± 1.5 (n=67)	/
IIEF	5.8 ± 2.9 (n=72)	5.9 ± 2.8 (n=75)	6.6 ± 2.7 (n=71)	6.5 ± 2.8 (n=68)	6.9 ± 3.0 (n=59)	/

USS-PROM, Patient-Reported Outcome Measure for Urethral Stricture Surgery; IPSS, International Prostate Symptom Score - Quality of Life; IIEF, International Index of Erectile Function; IIEF, International Index of Erectile Function – overall satisfaction domain; IIEF, International Index of Erectile Function – erectile function domain.

3.5.4 Comparison of balloon dilation with other endoluminal treatments

We conducted an analysis of two studies comparing DVIU and optical internal urethrotomy (OIU) and found no significant difference in efficacy between conventional balloon dilation and internal urethrotomy (RR=1.4754, 95%CI: 0.7306-2.9793; z=1.085, p=0.278; heterogeneity: I^2=0%, p=0.351) (Figure 2B). Even though fewer comparative studies are currently available, the balloon dilation may have potentially favorable long-term results by virtue of its smaller shear force and uniform 360° circumferential dilation. Yu, S. C. et al. reported that the estimated stricture-free survival rate at 12 months was 77.42% after balloon dilation and 48.00% after DVIU; moreover, a significantly higher stricture-free survival rate was observed in the balloon dilation group (P=0.02<0.05, HR=0.35, 95% CI for HR: 0.14–0.87) [31]. In Kumano, Y.'s study, the balloon dilation group had significantly longer stricture-free times than the optical internal urethrotomy group (p<0.01), with median (mean) stricture-free times of 1675 (1673) and 244 (599) days, respectively [30]. Currently, there are no studies comparing the clinical outcomes of simple dilation versus balloon dilation. Due to the paucity of current studies, no adequate evidence exists to suggest that balloon dilation is superior to other conventional endoluminal therapies.

3.6 Clinical preference and efficacy influencing factors of balloon dilation

3.6.1 Etiology

We pooled eight studies of simple balloon dilation that addressed specific etiologies [29-31, 33, 35-37, 41] involving a total of 307 patients. Iatrogenic urethral strictures (43.32%, 133/307) and idiopathic urethral strictures (34.20%, 105/307) accounted for the vast majority of cases. Stricture caused by trauma or inflammation accounted for 14.66% (45/307) and 6.51% (20/307), respectively. Four patients also suffered from radiation. Although this is only a one-sided epitome, it follows that iatrogenic injury may become the main etiology of urethral stricture in males in the future.

Due to the lack of meticulous subgroup analysis in the included studies, it was difficult for us to directly compare the differences in efficacy among strictures caused by different etiologies. The influence of etiology on the efficacy of balloon dilation depends primarily on the type of stenotic pathology it creates and the specific stenotic segment length and location. The essence of balloon dilation is the efficient expansion of the targeted site, taking care to avoid causing additional fibrosis of scar tissue in the narrow segment. If additional fibrosis occurs, strictures are highly likely to recur. Therefore, balloon dilation may not be suitable for strictures with a high degree of fibrosis. Lichen sclerosus is a specific cause of urethral stricture. The pathologic features of lichen sclerosus include hyperkeratosis or epithelial atrophy, basal cell vacuolar degeneration, lichenoid lymphocytic infiltration, and upper epithelial sclerosis [44]. This epithelial stromal lesion characterized by squamous atrophy or hyperplasia is distinct from the fibrotic pathologic characterization of most urethral strictures. A recent review pooling expert opinions in urology stated that dilation is unlikely to be a successful long-term solution for lichenoid sclerosing urethral stricture, potentially triggering adverse outcomes in the long term [45]. Balloon dilation is essentially a physical treatment method that cannot pathologically or fundamentally improve the condition of patients with specific urethral strictures, and its clinical indications need to be strictly controlled.

3.6.2 Location of the urethral stricture

We combined 11 studies that identified the location of the stricture [29, 32-41] ; 74.28% (488/657) were anterior urethral stricture, 21.77% (143/657) were posterior urethral stricture, and 3.95% (26/657) were both. Most patients who undergo balloon dilation are have anterior urethral stricture.

Most of the current studies have not further categorized comparisons of balloon dilation based on differences in stricture location, and the data of patients with stricture at different sites were analysed together. A subgroup analysis of eight conventional balloon dilation studies that involved the combination of success rates [31, 32, 34-36, 38-40] was performed according to the percentage of anterior urethral strictures, and the results are shown in Supplementary Figure 4. The combined results of studies with mostly anterior urethral strictures (70%-90%) reported a success rate of 66.45% (95% CI: 47.58%-83.01%) for balloon dilation.

Moreover, we combined data from two studies [32, 34] that included a subgroup analysis of stricture location and did not find any significant difference in the efficacy of balloon dilation between anterior and posterior urethral strictures (RR=0.9568, 95% CI: 0.6618-1.3832, p=0.814) (Figure 3A).

3.6.3 Length of urethral stricture

We previously performed a subgroup analysis of the pooled conventional balloon dilation success rate [31, 32, 34-36, 38-40] according to the length of the urethral stricture, and the results are shown in Figure 3B. For shorter strictures (≤ 2 cm), the success rate of balloon dilation reached 71.58% (95% CI: 61.93%-80.35%), and heterogeneity was also reduced (I^2=63.2342%, $p < 0.05$) (Figure 3B). In a study of

patients with anterior urethral strictures less than 1 cm in length, the success rate was as high as 85.7% [33]. The reduction in heterogeneity of the pooled results suggested that the stenotic segment length is a prognostic factor, and balloon dilation for short-segment urethral strictures may have a higher success rate.

3.6.4 Age

We further stratified the previous eight studies [31, 32, 34-36, 38-40] according to age group, and the results are shown in Figure 3C. In the 50- to 60-year-old age group, the success rate of balloon dilation was 80.79% (95% CI: 74.42%-86.47%). However, for patients older than 60 years, the success rate decreased to 58.49% (95% CI: 50.61%-66.17%). Interestingly, the combined success rate was 65.39% (95% CI: 39.61%-87.22%) in relatively young patients, probably because some of the reported younger patients had more severe strictures. The etiology of strictures in elderly patients is often iatrogenic, whereas in younger patients, more complex urethral strictures can be caused by relatively specific factors such as trauma and lichenoid sclerosis gonorrhoea. Even though the success rate is unclear, we can see a decreasing trend in the efficacy of balloon dilation in elderly patients.

3.6.5 Prior intervention management

A separate analysis of patients who had received prior endoscopic management (catheter/balloon dilation, direct visual internal urethrotomy) was performed in two studies [32, 34], and we found that balloon dilation had a pooled success rate of 49.51% (95% CI: 39.79%-59.26%) (Figure 3D). In patients who previously underwent surgical intervention, the efficacy of balloon dilation may be lower. Based on the limited data available in these two studies [32, 34], we compared the success rates of conventional balloon dilation in patients who did and did not undergo previous urethroplasty and found no significant difference (RR=1.1682, 95%CI: 0.6160-2.2153, p=0.634) (Supplementary Figure 5A). The prevailing clinical view is that repeated endoluminal intervention may render further endoluminal treatment less effective, but this needs to be confirmed by clinical studies with larger sample sizes.

3.6.6 Other patient status

We performed a more nuanced subgroup analysis of the two studies [32, 34] that provided some patient baseline details. There was no statistically significant difference in balloon dilation efficacy between patients with and without a smoking history (RR=1.1052, 95% CI: 0.8083-1.5112, p=0.531) (Supplementary Figure 5B). Chronic diseases such as coronary artery disease (RR=1.0714, 95% CI: 0.7618-1.5069, p=0.692), diabetes mellitus (RR=0.9144, 95% CI: 0.6118-1.3666, p=0.662), hypertension (RR=0.8377, 95% CI: 0.6121-1.1464, p=0.269), and chronic obstructive pulmonary disease (RR=1.3515, 95% CI: 0.7495-2.4374, p=0.317) did not significantly affect the efficacy of balloon dilation (Supplementary Figure 5C-F). Our preliminary analysis suggested that patient status, such as poor lifestyle habits and chronic diseases, may not significantly impact the efficacy of balloon dilation.

3.7 Intermittent urethral balloon self-dilation

Patient self-balloon dilation is a specific form of balloon dilation, and we also briefly review its clinical evaluation. Urethral dilation is easy to perform and can be performed by the patient at home, thereby avoiding the need for repeated hospitalizations and frequent general anaesthesia [46]. A study by Levine, L. A. [47] suggested that adjuvant balloon self-dilation at home may be a potential option for patients at high risk of recurrence. In this study of 25 eligible patients, most patients noted that balloon dilation improved voiding and maintained or improved the peak urinary flow rate at an average of 18.7 months after the initial procedure. Nonetheless, six patients (19%) complained of balloon placement discomfort, 3 (10%) noted minor bleeding during dilation, and 4 (13%) developed urinary tract infections during the follow-up period. Hennessey, D. B. 's initial experience with self-expanding balloon dilation in the outpatient setting was encouraging, with all 11 patients reporting that they were very satisfied or satisfied with their overall outcomes and quality of life [48]. A recent study reported in 2021 stated that self-urethral balloon dilation offers patients with complex strictures, especially those with a history of radiation, an opportunity to avoid surgical intervention [49].

However, the imprecision of patient self-balloon dilation may cause complications and even aggravate injury. As early as the last century, scholars have shown that short-term postoperative self-dilation techniques do not appear to prevent stricture recurrence in patients treated with endourethral incisions [50]. A meta-analysis of patient self-dilation also indicated that the quality of evidence for this approach to reduce the risk of recurrent urethral strictures is very low [51]. Although self-dilation is very convenient and avoids surgical complications, it is not suitable for all patients, and not all patients can master the skills and techniques of self-dilation. Self-dilation needs to be further weighed against surgery, and well-designed randomized controlled trials are needed to determine whether this benefit of convenience is sufficient to make this intervention worthwhile.

4. Discussion

With the gradual increase in the incidence of iatrogenic urethral strictures, surgeons should choose the appropriate treatment method according to the etiology of the urethral stricture, the location and length of the stricture, and the degree of urethral fibrosis. Even though there is no clear evidence that the clinical efficacy of balloon dilation is significantly better than that of other endoluminal treatments, such as simple dilation and DVIU, balloon dilation still has high clinical plasticity.

Both balloon dilation and simple dilation are essentially dilatation, causing tearing of scar tissue and scar remodelling at the site of the stricture. Balloon dilation involves the application of a 360° circumferential radial force at the stricture site, providing a more uniform force than simple dilation. Moreover, for harder scars that cannot be torn by simple dilation, the pressure of the balloon can be gradually increased to achieve dilatation, which has broader clinical indications.

Urethrotomy requires a radial incision at the site of the stricture. The main

disadvantage of internal urethrotomy is the inability to accurately estimate the depth of scar tissue during the procedure, resulting in imprecise scar tissue incisions. There may also be damage to the corpus cavernosum below the urethra, and vascular disruption in the corpus cavernosum and localized extravasation of urine through mucosal fissures may exacerbate corpus cavernosum fibrosis, eventually leading to stricture recurrence [31, 52]. Some scholars believe that balloon dilation tends to be performed in fewer fibrotic cases without urethral cavernous fibrosis, suggesting that balloon dilation will not invade the deep urethral membrane; therefore, even if the dilation time is longer, the restenosis rate of balloon dilation is lower than that of optical internal urethrotomy [30]. Thus, DVIU is commonly used for posterior urethral strictures and is avoided in the penile urethra to prevent leakage of the cavernous penile veins to circumvent the risk of causing impotence. Balloon dilation has no definitive stricture site limitations and can be effective in the dilatation of hard-textured scars that cannot be incised by DVIU. Yu, S. C. et al. reported that the operation time of balloon dilation was much shorter than that of DVIU (13.19±2.68 min vs. 18.44±3.29 min, $P<0.01$) [31], highlighting the operational simplicity of balloon dilation. Compared with urethrotomy, balloon dilation has a lower cost and can improve the efficiency of hospital bed turnover [53].

To reduce the high recurrence rate after endoluminal treatment, intraurethral lesion injections of drugs such as steroids and mitomycin C are commonly used, and balloons are considered promising forms of drug delivery [54]. The advent and use of drug-coated balloons can reduce inflammation and relapse rates by releasing drugs such as immunosuppressants during expansion. Barbalias, D. et al. conducted animal experiments using paclitaxel-coated balloons and reported that paclitaxel could pass through the urothelial barrier and immediately distribute to the urothelium, submucosa and smooth muscle layers of the normal rabbit urethra after dilation [55]. The drug can penetrate the epithelium and act on deep urethral tissue, effectively reducing inflammation and inhibiting urethral fibrosis. In the recent ROBUST I study [28], an optilume drug-coated balloon (DCB) was shown to maintain symptom relief for 3 years after treatment in a highly susceptible population with recurrent urethral strictures. The 43 patients in this trial had a functional success rate of 67%, a retreatment-free rate of 77%, and an improvement in the mean IPSS from 25.2 at baseline to 5.5 at 3 years ($p<0.0001$). The 1-year results from another RCT (the ROBUST III study) [27] showed that patients dilated with an optilume DCB had a significantly higher anatomical success rate at 6 months than those in the DVIU group (75% vs. 27%, $p<0.001$). Both the symptoms and urinary flow rates improved significantly in both groups, but these effects were significantly more pronounced in the Optilume DCB group. The United States Food and Drug Administration (FDA) has approved the use of the Optilume drug-coated balloon for the treatment of male urethral strictures [56]. Nevertheless, in the ROBUST III study [27], the incidences of serious adverse events in the control group (DVIU/simple dilation) and DCB group were 16.7% and 10.1%, respectively. The types and incidences of adverse events in the two groups were closely matched, but the incidences of postoperative haematuria and dysuria were higher in the DCB group than in the control group (11.4% and 2.1%,

respectively). In addition, Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation is expected to delay stricture recurrence in patients with urethral strictures. A clinical report of five patients revealed that the mean treatment interval was prolonged from 2.2 months to 10.7 months after Rhenium-188 mercaptoacetyltriglycine-filled balloon dilation [57]. Further consideration needs to be given to factors such as the local drug concentration achievable in dilation and the reliability of the therapeutic dose. The design of new balloons, such as cutting balloons, and the exploration of new expansion techniques may be research directions in the future [58, 59]. The new type of balloon should meet the biomechanical requirements to better fit the narrow urethra.

The timing of balloon dilation is closely related to the location, length, and scar thickness of the stricture, and appropriate case selection is critical. Balloon dilation may be an intermediate step before urethroplasty and is a promising alternative therapy to simple dilation and urethrotomy. Like simple dilation and DVIU, balloon dilation is indicated for patients with short-segment urethral strictures. Although balloon dilatation is currently not definitively superior to simple dilation or DVIU due to the lack of long-term follow-up studies, balloon dilation has the following advantages: (1) In principle, the balloon expands with less shear force, presenting a gradual uniform 360° circular dilation so as to minimize the non-therapeutic urethral injuries; (2) In the penile urethra where DVIU is not recommended, simple dilation and balloon dilation can be used; (3) As long as the guidewire can be passed, simple dilation and balloon dilation can be attempted in stenotic segments in which the endoscope of the DVIU cannot pass; (4) The balloon, with its high pressure, can dilate some urethras with harder scars that are difficult to dilate with simple dilation and DVIU; (5) The balloon can be used as a promising drug delivery tool and has achieved favourable clinical results. For some patients with long complex urethral strictures, balloon dilation may even be used as an initial therapy. In patients with recurrent strictures, urethrotomy or urethral dilation followed by urethroplasty has been shown to be the most cost-effective strategy [60]. The use of endoscopic urethroplasty combined with balloon dilation for traumatic destruction of the prostatic membranous urethra has been previously reported [61]. Balloon dilation can also be used in conjunction with repeat simple dilation, endourethrotomy and urethroplasty. If urethroplasty is not feasible, patients can undergo intermittent self-dilation to stabilize the results after endoluminal therapy. Intermittent urethral balloon self-dilation may be an option, but its safety is difficult to ensure due to the lack of direct visualization control and difficulty in achieving the appropriate therapeutic pressure of the balloon. There is no standardized schedule for self-dilation, and the exact dilation schedule depends on the condition and the treatment recommended by the doctor. Patients are usually advised to start with more frequent dilation, even daily, and then gradually increase the interval. Intermittent self-dilation can continue for a fixed period of time or indefinitely. Nevertheless, intermittent self-dilation tends to stabilize the stricture and prolong recurrence rather than keep the patient stricture free [3]. The emergence of a new, safer, drug-coated balloon suitable for at-home use may prolong the patient self-dilation interval and bring new hope for future treatments.

We recognize the limitations of our research. There is a considerable risk of bias in this meta-analysis, most of which stems from the retrospective design of the studies and the lack of valid controls. Evidence from retrospective observational studies needs to be interpreted with caution because of the susceptibility to selection bias, recall bias, and exaggerated efficacy of balloon dilation. The assessment of the efficacy of balloon dilation is often subjective, and it is difficult to use a clear objective measure. Patients have different perceptions of their voiding status, and patients' subjective feelings can influence their choice of therapeutic intervention. The efficacy of balloon dilation is also affected by confounding factors such as etiology, stricture location, stricture length, prior management intervention, comorbidities and socioeconomic status. The long-term outcomes of balloon dilation need to be further investigated. RCTs with larger sample sizes and more comparable control groups are needed to further prove the efficacy and safety of balloon dilation in the future.

5. Conclusion

Balloon dilation may be an intermediate step before urethroplasty and a promising alternative to simple dilation and DVIU. The balloon is a promising drug delivery tool, and paclitaxel drug-coated balloon dilation is effective in reducing retreatment rates in patients with recurrent anterior urethral strictures. Due to the low quality of the evidence, we have little confidence in our estimates of effects. Evidence for other comparisons and outcomes is also limited. The stricture etiology, stricture location, stricture length, and previous treatment may be associated with the efficacy of balloon dilation. However, additional high-quality studies are needed for further investigation.

Contribution Statement

Conceptualization was created by X.L and C.X. Investigation was performed by X.L, X.J, and C.X. Analysis and interpretation of data were produced by X.L, X.J and C.X. X.L and C.X wrote the manuscript. X.L and X.J conducted the statistical analysis. Critical revision of the manuscript for important intellectual content was produced by X.L, C.X, Z.Z, T.C, Z.G and J.L. Supervision was performed by J.L.

Acknowledgement

None.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Statement of Ethics

The outcome of this meta-analysis could improve clinical decision and help to reduce the risk and cost of patients. All patients included in this study have signed informed consent during the course of each trial. And specific methods of assessment in each trial have been illustrated above. This systematic review did not any addition intervention to all included individuals. Thanks to all the patients and researchers included for their contribution to this study.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Figure 1: Flow diagram of study selection.

Figure 2: Forest plots showing the efficacy of balloon dilation. (A) Success rate of conventional balloon dilation; (B) Balloon dilation (Drug-coated balloons excluded) compared with simple dilation, DVIU, and optical internal urethrotomy (OIU). CI, confidence interval.

Figure 3: Forest plots showing the possible influencing factors of balloon dilation. (A) Location of the urethral stricture; (B) Length of urethral stricture; (C) Age; (D) Prior endoscopic management. CI, confidence interval.

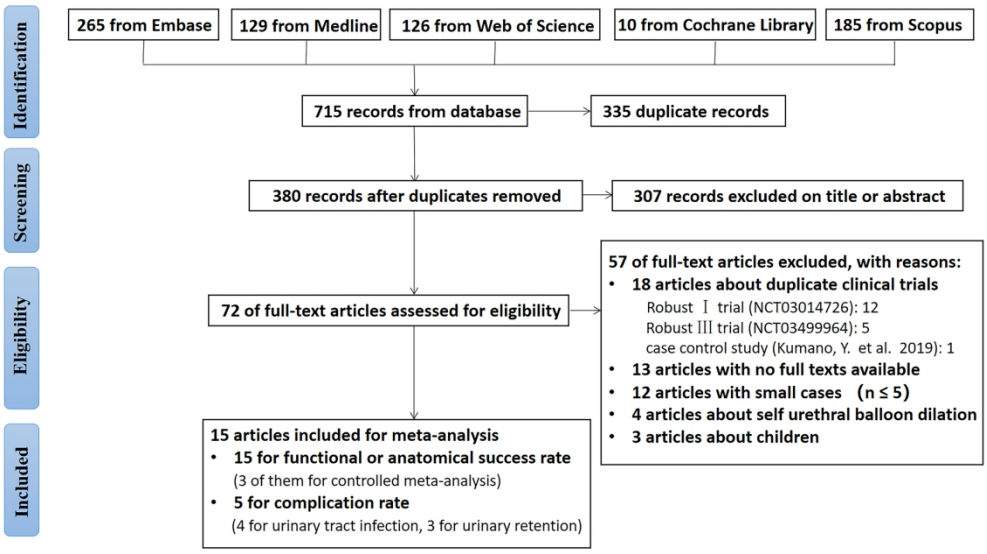

Figure 1: Flow diagram of study selection.

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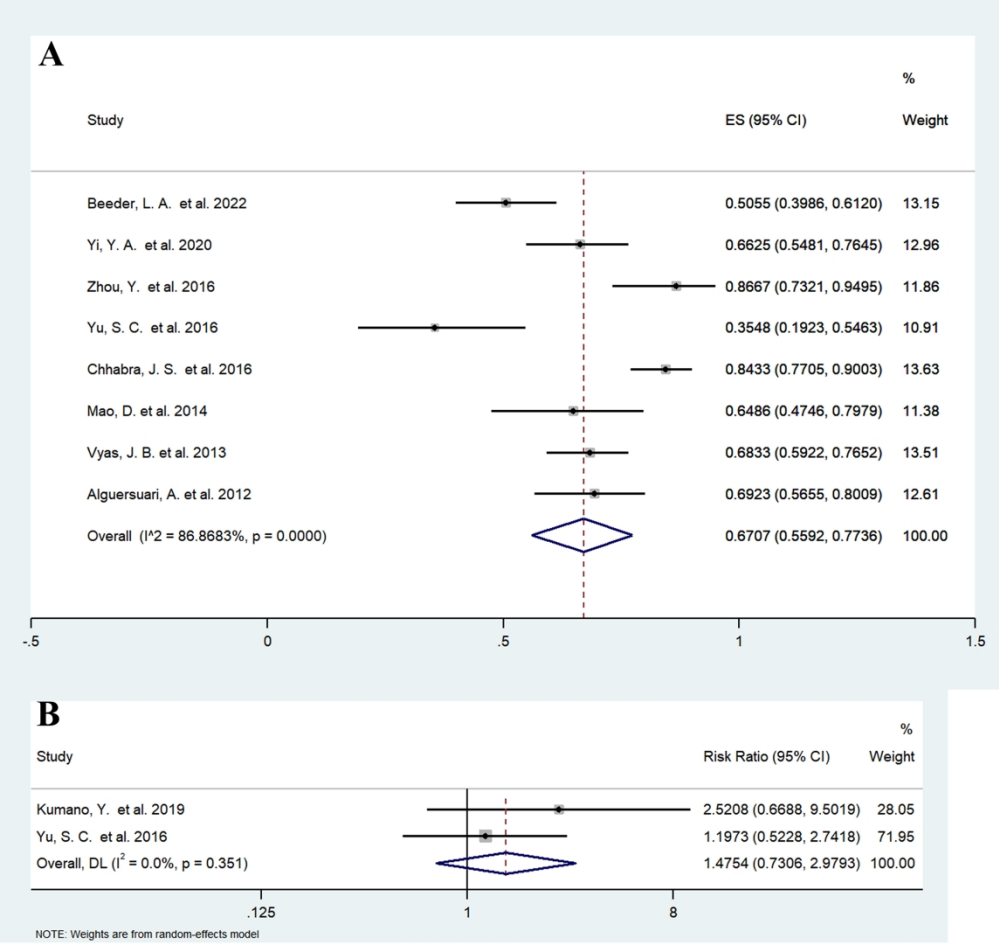

Figure 2: Forest plots showing the efficacy of balloon dilation. (A) Success rate of simple balloon dilation; (B) Balloon dilation (Drug-coated balloons excluded) compared with simple dilation, DVIU, and optical internal urethrotomy (OIU). CI, confidence interval.

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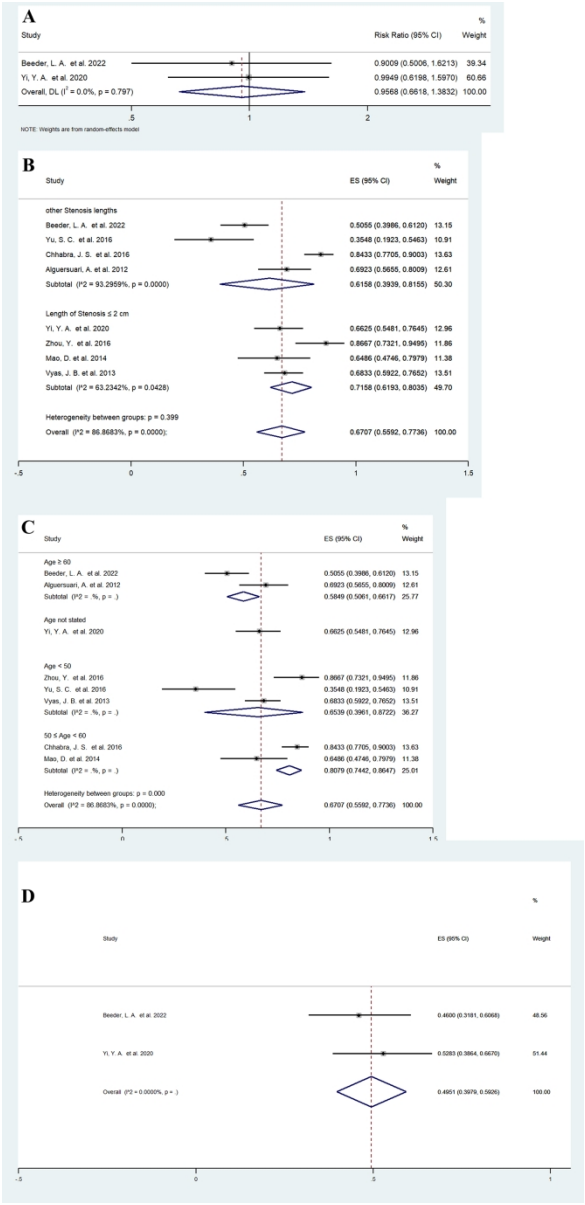

Figure 3: Forest plots showing the possible influencing factors of balloon dilation. (A) Location of urethral stricture; (B) Length of urethral stricture; (C) Age; (D) Prior endoscopic management. CI, confidence interval.

144x297mm (300 x 300 DPI)

Supplementary File. Search strategy

(Urethral Stricture OR Stricture, Urethral OR Strictures, Urethral OR Urethral Strictures OR Urethral Stenosis OR Stenoses, Urethral OR Stenosis, Urethral OR Urethral Stenoses OR Anterior Urethral Stricture OR Anterior Urethral Strictures OR Urethral Strictures, Anterior OR Urethral Stricture, Anterior OR Posterior Urethral Stricture OR Posterior Urethral Strictures OR Urethral Strictures, Posterior OR Urethral Stricture, Posterior) AND (Dilatation OR Dilatations OR Dilation OR Dilations) AND (Balloon)

MEDLINE

#1. TS=(Urethral Stricture OR Stricture, Urethral OR Strictures, Urethral OR Urethral Strictures OR Urethral Stenosis OR Stenoses, Urethral OR Stenosis, Urethral OR Urethral Stenoses OR Anterior Urethral Stricture OR Anterior Urethral Strictures OR Urethral Strictures, Anterior OR Urethral Stricture, Anterior OR Posterior Urethral Stricture OR Posterior Urethral Strictures OR Urethral Strictures, Posterior OR Urethral Stricture, Posterior)
#2. TS=(Dilatation OR Dilatations OR Dilation OR Dilations)
#3. TS=(Balloon)
#1 AND #2 AND #3

Web of Science (WOS)

#1. TS=(Urethral Stricture OR Stricture, Urethral OR Strictures, Urethral OR Urethral Strictures OR Urethral Stenosis OR Stenoses, Urethral OR Stenosis, Urethral OR Urethral Stenoses OR Anterior Urethral Stricture OR Anterior Urethral Strictures OR Urethral Strictures, Anterior OR Urethral Stricture, Anterior OR Posterior Urethral Stricture OR Posterior Urethral Strictures OR Urethral Strictures, Posterior OR Urethral Stricture, Posterior)
#2. TS=(Dilatation OR Dilatations OR Dilation OR Dilations)
#3. TS=(Balloon)
#1 AND #2 AND #3

EMBASE

#1. 'Stricture, Urethral':ab,ti OR 'Strictures, Urethral':ab,ti OR 'Urethral Strictures':ab,ti OR 'Urethral Stenosis':ab,ti OR 'Stenoses, Urethral':ab,ti OR 'Stenosis, Urethral':ab,ti OR 'Urethral Stenoses':ab,ti OR 'Anterior Urethral Stricture':ab,ti OR 'Anterior Urethral Strictures':ab,ti OR 'Urethral Strictures, Anterior':ab,ti OR 'Urethral Stricture, Anterior':ab,ti OR 'Posterior Urethral Stricture':ab,ti OR 'Posterior Urethral Strictures':ab,ti OR 'Urethral Strictures, Posterior':ab,ti OR 'Urethral Stricture, Posterior':ab,ti
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#3. 'Balloon':ab,ti
#1 AND #2 AND #3

Cochrane Library

#1. (Urethral Stricture):ti,ab OR (Strictures, Urethral):ti,ab OR (Stricture, Urethral):ti,ab OR (Urethral Strictures):ti,ab OR (Urethral Stenosis):ti,ab OR (Stenoses, Urethral):ti,ab OR (Stenosis, Urethral):ti,ab OR (Urethral Stenoses):ti,ab OR (Anterior Urethral Stricture):ti,ab OR (Anterior

Urethral Strictures):ti,ab OR (Urethral Strictures, Anterior):ti,ab OR (Urethral Stricture, Anterior):ti,ab OR (Posterior Urethral Stricture):ti,ab OR (Posterior Urethral Strictures):ti,ab OR (Urethral Strictures, Posterior):ti,ab OR (Urethral Stricture, Posterior):ti,ab
#2. (Dilatations):ti,ab OR (Dilatation):ti,ab OR (Dilation):ti,ab OR (Dilations):ti,ab
#3. (Balloon):ti,ab
#1 AND #2 AND #3

Scopus
#1. TITLE-ABS-KEY("Urethral Stricture" OR "Stricture, Urethral" OR "Strictures, Urethral" OR "Urethral Strictures" OR "Urethral Stenosis" OR "Stenoses, Urethral" OR "Stenosis, Urethral" OR "Urethral Stenoses" OR "Anterior Urethral Stricture" OR "Anterior Urethral Strictures" OR "Urethral Strictures, Anterior" OR "Urethral Stricture, Anterior" OR "Posterior Urethral Stricture" OR "Posterior Urethral Strictures" OR "Urethral Strictures, Posterior" OR "Urethral Stricture, Posterior")
#2. TITLE-ABS-KEY("Dilatation" OR "Dilatations" OR "Dilation" OR "Dilations")
#3. TITLE-ABS-KEY("Balloon")
#1 AND #2 AND #3

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4, 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4, 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4, 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4, 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4, 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6, 7, 8, 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6, 7, 8, 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6, 7, 8, 9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	6, 7, 8, 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6, 7, 8, 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6, 7, 8, 9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	10
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	10, 11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2, 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2, 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	12

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2: The main characteristics of included studies.

Study	Year	Country	Type of Study	Article Type	NOS Score（0-9）	Jadad Score（0-7）	MINORS Score（0-24）
Virasoro, Ramon et al.	2022	USA, Dominican Republic, Panama	Single-arm Clinical Trial	Journal article	/	/	10
Elliott, S. P. et al.	2022	USA, Canada	RCT	Journal article	/	5	/
Beeder, L. A. et al.	2022	USA	Retrospective Case Study	Journal article	3	/	/
Alibekov, M. M. et al.	2021	Russia	Retrospective Case Study	Journal article	2	/	/
Yi, Y. A. et al.	2020	USA	Retrospective Case Study	Journal article	3	/	/
Kumano, Y. et al.	2019	Japan	Case Control Study	Journal article	5	/	/
Zhou, Y. et al.	2016	China	Retrospective Case Study	Journal article	2	/	/
Yu, S. C. et al.	2016	China	Case Control Study	Journal article	6	/	/
Chhabra, J. S. et al.	2016	India	Retrospective Case Study	Journal article	3	/	/
Ishii, Gen et al.	2015	Japan	Retrospective Case Study	Journal article	3	/	/
Mao, D. et al.	2014	China	Retrospective Case Study	Journal article	2	/	/
Vyas, J. B. et al.	2013	India	Retrospective Case Study	Journal article	3	/	/
Alguersuari, A. et al.	2012	Spain	Retrospective Case Study	Conference abstract	2	/	/
MacDiarmid, S. A. et al.	2000	USA	Retrospective Case Study	Journal article	2	/	/
Mohammed, S. H. et al.	1988	Denmark	Single-arm Clinical Trial	Journal article	/	/	6

NOS, Newcastle Ottawa Scale; MINORS, Methodological Index for Non-randomized Studies.

Supplementary Table 3A. Description and decision criteria for each domain in ROBINS-I

Bias domain	Explanation	Judgments
Bias due to confounding	1. Is there potential for confounding of the effect of intervention in this study? 2. Did the authors use a multivariable-adjusted analysis method that controlled at least for the important confounding domains (age, body mass index, etiology, location of the stricture, length of the stricture, prior intervention management, others) ? 3. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? 4. Did the authors control for any post-intervention variables that could have been affected by the intervention? 5. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? 6. Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	1. Low risk of bias: No bias expected due to confounding, including time-varying confounding. 2. Moderate risk of bias: Confounding is expected: including at least 5 factors of the following factors: age, body mass index, etiology, location of the stricture, length of the stricture, prior intervention management, others (i.e. comorbidities, socio-economic status) and have been appropriately controlled for in a multivariable-adjusted analysis. 3. Serious risk of bias: 3-4 above-mentioned factors were measured or appropriately controlled for. 4. Critical risk of bias: less than 3 above-mentioned factors were measured or appropriately controlled for. 5. No information: No information on which confounders have been controlled for.
Bias in selection of participants into the study	1. Was selection of participants into the study based on participant characteristics observed after the start of intervention? 2. Were the post-intervention variables that influenced selection likely to be associated with intervention? 3. Were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? 4. Do start of follow-up and start of intervention coincide for most participants? 5. Were adjustment techniques used that are likely to correct for the presence of selection biases?	1. Low risk of bias: All participants who would have been eligible for the target study were included in the study. 2. Moderate risk of bias: Selection into the study may have been related to exposure and outcome and the authors used appropriate methods to correct for the selection bias. 3. Serious risk of bias: Selection into the study was related to intervention and outcome and this could not be corrected for in the analyses; or the start of follow-up and start of exposure do not coincide and the rate ratio is not constant over time. 4. Critical risk of bias: Selection into the study was very strongly related to intervention and outcome and this could not be corrected for in the analyses; or a substantial amount of follow-up time is likely to be missing from analyses 3.the rate ratio is not constant over time. 5. No information: No information is reported about

		selection of participants into the study.
Bias in classification of interventions	1. Were intervention groups clearly defined? 2. Was the information used to define intervention groups recorded at the start of the intervention? 3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	1. Low risk of bias: The patient clearly underwent urethral balloon dilation, and no measurement error is expected in its assessment. 2. Moderate risk of bias: Intervention status is well defined and some aspects of the assignments of intervention status were determined retrospectively. 3. Serious risk of bias: Intervention status is not well defined; or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome. 4. Critical risk of bias: An extremely high amount of misclassification of intervention status (i.e. because of unusually strong recall biases). 5. No information: No definition of the intervention or no explanation of the source of information about intervention status is reported.
Bias due to deviations from intended interventions	1. Were there deviations from the intended intervention beyond what would be expected in usual practice? 2. Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	1. Low risk of bias: Patients did not receive other invasive urethral stricture treatments between the time they underwent balloon dilatation and the follow-up period to assess success. 2. Moderate risk of bias: There were deviations from usual practice, but their impact on the outcome is expected to be slight. 3. Serious or critical risk of bias: There were deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. 4. Critical risk of bias: There were substantial deviations from usual practice that were unbalanced between the intervention groups and likely to have affected the outcome. 5. No information: No information on deviations from the intervention is reported.
Bias due to missing data	1. Were outcome data available for all, or nearly all, participants? 2. Were participants excluded due to missing data on intervention status? 3. Were participants excluded due to missing data on other variables needed for the analysis? 4. Are the proportion of participants and reasons for missing data similar across	1. Low risk of bias: Little loss-to-follow-up and data on intervention and other variables were reasonably complete (<10% missing data) and was unlikely to introduce bias; or the analysis addressed missing data and is likely to have removed any risk of bias. 2. Moderate risk of bias: There is a proportion of missing data in the original cohort or a high proportion of loss-to-follow-up; and the analysis is unlikely to have removed the risk of bias arising

	interventions? 5. Is there evidence that results were robust to the presence of missing data?	from the missing data (i.e. using logistic regression). 3. Serious risk of bias: High proportions (>50%) of missing data; and the analysis is unlikely to have removed the risk of bias arising from the missing data; or missing data were addressed inappropriately in the analysis; or the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis. 4. Critical risk of bias: There were critical differences between interventions in participants with missing data; and missing data were not, or could not, be addressed through appropriate analysis. 5. No information: No information is reported about missing data or the potential for data to be missing.
Bias in measurement of outcomes	1. Could the outcome measure have been influenced by knowledge of the intervention received? 2. Were outcome assessors aware of the intervention received by study participants? 3. Were the methods of outcome assessment comparable across intervention groups? 4. Were any systematic errors in measurement of the outcome related to intervention received?	1. Low risk of bias: The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention status of study participants; and any error in measuring the outcome is unrelated to intervention status (i.e., objective measures such as confirmed medical records, record linkage). 2. Moderate risk of bias: The methods of outcome assessment were comparable across intervention groups; and any error in measuring the outcome may be minimally related to intervention status or if the outcome measure was not reliable measured (i.e. confirmed records are not available for the whole study population). 3. Serious risk of bias: The methods of outcome assessment were not comparable across intervention groups; or the outcome measure was subjective (i.e. vulnerable to influence by knowledge of the intervention received by study participants); and error in measuring the outcome was related to intervention status. 4. Critical risk of bias: The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups. 5. No information: No information is reported about the methods of outcome assessment.
Bias in selection of the reported result	1. Is the reported effect estimate likely to be selected from multiple analyses of the intervention-outcome relationship?	1. Low risk of bias: There is a clear description of all analyses and the analyses are consistent and all reported results correspond to all intended outcomes,

	2. Is the reported effect estimate likely to be selected from different subgroups?	analyses and sub-cohorts. 2. Moderate risk of bias: The analyses are clearly defined; and there is an indication of selection of the reported analysis from among multiple analyses; and there is an indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results (i.e. estimates not shown for all analyses). 3. Serious risk of bias: There is a high risk of selective reporting from among multiple analyses; or the cohort or subgroup is selected from a larger study for analysis and appears to be reported based on the results. 4. Critical risk of bias: There is evidence or strong suspicion of selective reporting of results; and the unreported results are likely to be substantially different from the reported results. 5. No information: There is too little information to make a judgment.

Overall judgment

1. Low risk of bias

The study is judged to be at a low risk of bias for all domains.

2. Moderate risk of bias

The study is judged to be at low or moderate risk of bias for all domains.

3. Serious risk of bias

The study is judged to be at serious risk of bias in at least one domain, but not at critical risk in any domain.

4. Critical risk of bias

The study is judged to be at critical risk of bias in at least one domain.

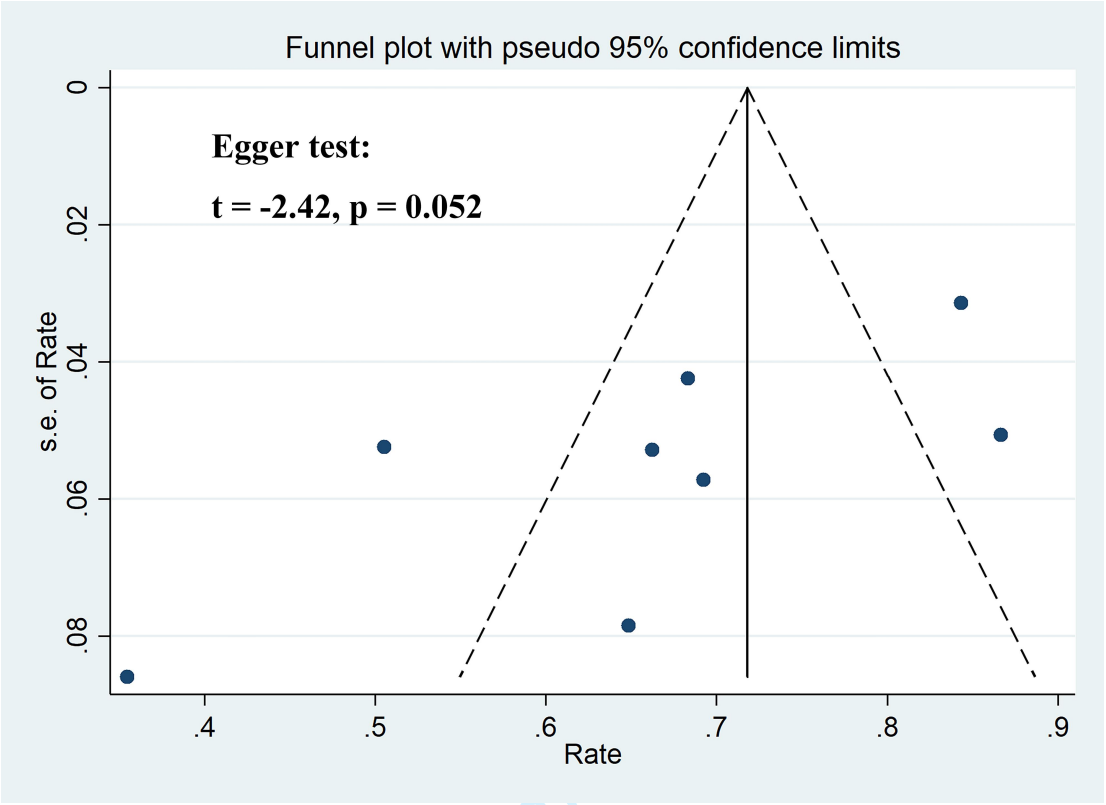
Supplementary Table 3B. Quality assessment results using the ROBINS-I tool

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall judgment
Virasoro, Ramon et al. 2022	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Beeder, L. A. et al. 2022	Moderate	Serious	Moderate	Low	Low	Serious	Moderate	Serious
Alibekov, M. M. et al. 2022	Serious	Serious	Moderate	Low	Low	Serious	Serious	Serious
Yi, Y. A. et al. 2020	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Kumano, Y. et al. 2019	Serious	Serious	Moderate	Low	Low	Serious	Moderate	Serious
Zhou, Y. et al. 2016	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Yu, S. C. et al. 2016	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Chhabra, J. S. et al. 2016	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Ishii, Gen et al. 2015	Serious	Critical	Moderate	Low	Low	Serious	Moderate	Critical
Mao, D. et al. 2014	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Vyas, J. B. et al. 2013	Serious	Serious	Moderate	Low	Low	Moderate	Moderate	Serious
Alguersuari, A. et al. 2012	Serious	Serious	Moderate	Low	Low	Serious	Serious	Serious
MacDiarmid, S. A. et al. 2000	Serious	Serious	Moderate	Low	Moderate	Serious	Moderate	Serious
Mohammed, S. H. et al. 1988	Critical	Serious	Low	Low	Moderate	Serious	Serious	Critical

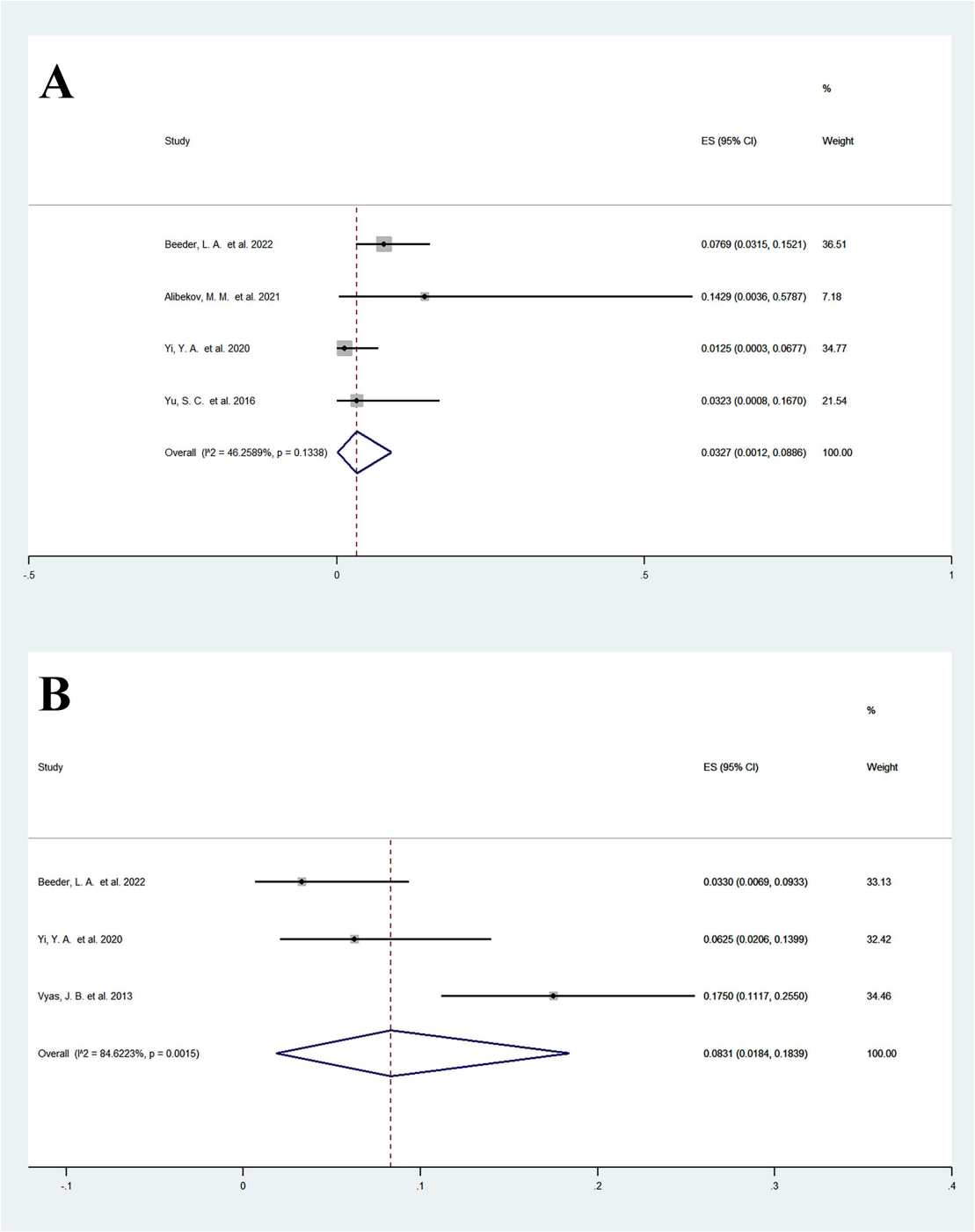
Supplementary Table 4: Sensitivity analysis of the pooled results of conventional balloon dilation success rate.

Excluded Study	Pooled Results (%)	95% Confidence Interval	
Beeder, L. A. et al. 2022	69.57	58.61	79.55
Yi, Y. A. et al. 2020	67.12	54.10	78.96
Zhou, Y. et al. 2016	64.13	52.45	75.03
Yu, S. C. et al. 2016	70.64	60.47	79.90
Chhabra, J. S. et al. 2016	64.05	53.49	73.99
Mao, D. et al. 2014	67.31	54.95	78.59
Vyas, J. B. et al. 2013	66.76	53.20	79.09
Alguersuari, A. et al. 2012	66.69	53.81	78.45

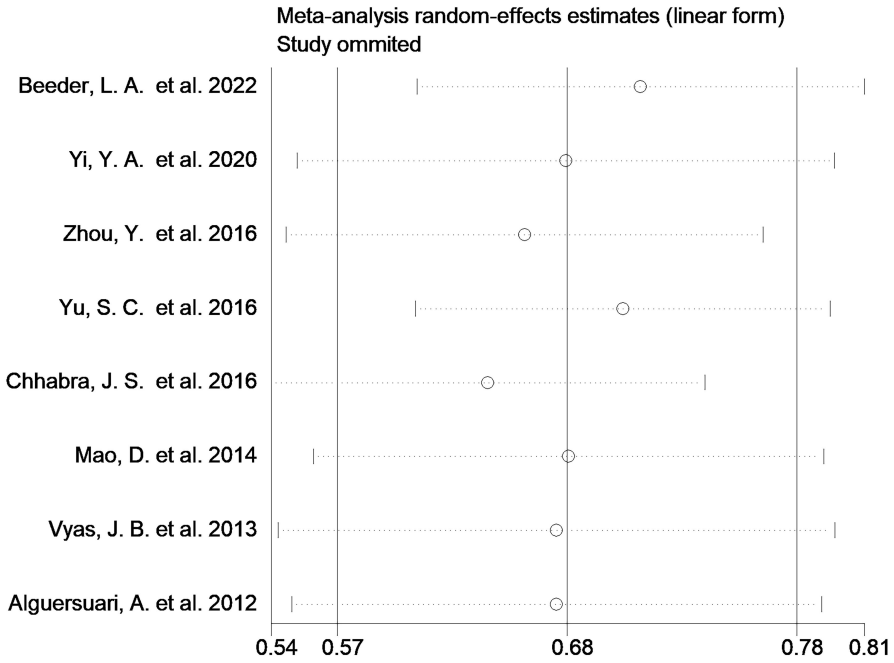
Supplementary Figure 1: The funnel plot of conventional balloon dilation success rate.



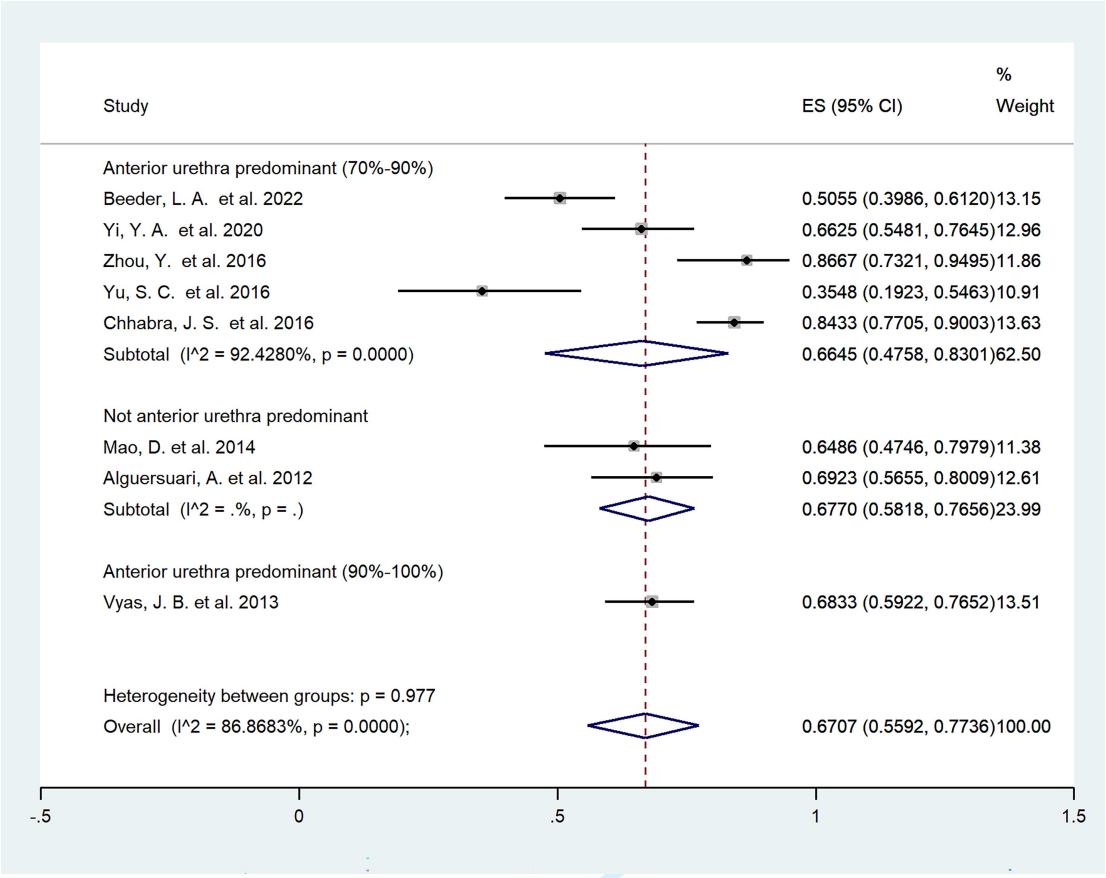
Supplementary Figure 2: Forest plots showing the safety of balloon dilation. (A) Incidence of infection; (B) Incidence of urinary retention. CI, confidence interval.



Supplementary Figure 3: The sensitivity analysis of conventional balloon dilation success rate.



Supplementary Figure 4: Forest plots showing the subgroup analysis of conventional balloon dilation success rate according to the percentage of anterior urethral strictures.



Supplementary Figure 5: Forest plots showing other possible influencing factors of balloon dilation. (A) with and without previous urethroplasty; (B) History of smoking; (C) Coronary heart disease; (D) Diabetes mellitus; (E) Hypertension; (F) Chronic obstructive pulmonary disease. CI, confidence interval.