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Risk calculator for prediction of treatment-related urethroplasty failure in patients with penile urethral strictures

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Abstract

Purpose To design a dedicated risk calculator for patients with penile urethra stricture who are scheduled to urethroplasty that might be used to counsel patients according to their pre-operative risk of failure.

Methods Patients treated with penile urethroplasty at our center (1994–2018) were included in the study. Patients received 1-stage or staged penile urethroplasty. Patients with failed hypospadias repair, lichen sclerosus or incomplete clinical records were excluded. Treatment failure was defined as any required postoperative instrumentation, including dilation. Univariable Cox regression identified predictors of post-operative treatment failure and Kaplan–Meier analysis plotted the failure-free survival rates according to such predictors. Multivariable Cox regression-based risk calculator was generated to predict the risk of treatment failure at 10 years after surgery.

Results 261 patients met the inclusion criteria. Median follow-up was 113 months. Out of 216 patients, 201 (77%) were classified as success and 60 (23%) failures. Former smoker (hazard ratio [HR] 2.12, $p=0.025$), instrumentation-derived stricture (HR 2.55, $p=0.006$), and use of grafts (HR 1.83, $p=0.037$) were predictors of treatment failure. Model-derived probabilities showed that the 10-year risk of treatment failure varied from 5.8 to 41.1% according to patient's characteristics.

Conclusions Long-term prognosis in patients who underwent penile urethroplasty is uncertain. To date, our risk-calculator represents the first tool that might help physicians to predict the risk of treatment failure at 10 years. According to our model, such risk is largely influenced by the etiology of the stricture, the use of graft, and patient's smoking habits.

Keywords Penile urethra · Urethroplasty · Oral mucosa · Multivariable statistical analysis · Risk calculator

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Abbreviations

QoL	Quality of life
BMI	Body mass index
FHR	Failed hypospadias repair
LS	Lichen sclerosus
RUG	Retrograde urethrogram
VCUG	Voiding cystourethrogram
PVR	Post-void residual

Introduction

Basically, the surgical treatment of penile strictures is reported in the literature as a part of anterior urethral stricture repair [1]. Strictures involving the external urinary meatus, the navicularis or penile urethra greatly differ from bulbar strictures with respect to their etiology, anatomy, and characteristics, involving not only functional but the aesthetic aspect also [1–4]. Strictures of penile urethra don't respond successfully to dilation or urethrotomy, and patients are candidates to reconstructive surgery [5]. For many years, the use of one-stage penile skin flap urethroplasty and two-stage repair, represented the gold-standard surgical approach in penile stricture repair. Later, the widespread use of oral mucosa for urethral reconstruction in hypospadias repair and bulbar urethra, opened a new era also in penile one or two-stage urethroplasty [6–9]. The spectrum of penile urethral strictures is very broad for anatomical and pathological reasons, including strictures (meatus, navicularis fossa, and penile urethra) each presenting peculiar features, and different morphology and characteristics [2–5]. Many factors must be taken into account when the surgeon discusses with the patient about indication for one or two-stage repair. Some patient's features: age, psychological involvement in the disease, quality of life (QoL) and social life, marital status, body mass index (BMI), smoking habits, diabetes and other comorbidity, glans and foreskin appearance, may play an important role into making decision for one-stage vs. staged repair. Some stricture's features: etiology, length, obliterative vs non-obliterative stricture, history of previous failed surgical repair, may also greatly influence the indication for one vs. staged repair. Surgeon features or preferences: background on tissue transfer procedures, current use of oral mucosa graft for urethroplasty, functional vs. aesthetic outcome, and more, may play a role into making decision [2–4]. For all these reasons patient counseling is pivotal regarding the surgical strategy and prediction of outcome. Risk calculators have been developed for prediction of lymph node positive disease in patients with prostate cancer and they assist urologist in decision making [10]. So far, to our best knowledge, none have developed similar tools for urethral stricture disease. In the current paper, we attempted to develop a dedicated risk calculator for patients with penile urethra stricture who are scheduled to urethroplasty.

Materials and methods

Study design and patient population

We performed a retrospective descriptive analysis of patients treated with penile urethroplasty at our institution, between Apr. 1994 to Feb. 2018. Follow-up was calculated for each patient based on time from surgery to the last office follow-up. Inclusion criteria consisted of patients treated with 1-stage or staged penile urethroplasty with 12 months' minimum follow-up. Patients with failed hypospadias repair (FHR), lichen sclerosus (LS) or incomplete clinical records were excluded. The primary outcome of the study was the postoperative failure-free survival in the overall population, with the identification of success/failure for any single technique. The secondary outcomes of the study were the identification of significant predictors of treatment failure and the development of a corresponding risk calculator.

Variables of interest and study outcomes

Preoperative data included age, clinical history, retrograde urethrogram (RUG), voiding cystourethrogram (VCUG), and post-void residual (PVR). Clinical history consisted of stricture etiology, and previous treatments. RUG, VCUG, urethral ultrasound were used to assess the stricture site and length. Clinical outcome was considered a failure when any postoperative instrumentation was needed, including dilation. Uroflowmetry and urine culture were repeated every 6 months in the first 2 years and annually thereafter. When symptoms of decreased force of stream were present and the uroflowmetry was less than 12 ml/s, RUG, VCUG, PVR, urethral ultrasound and urethroscopy were repeated to identify the recurrent stricture.

Description of the surgical techniques

In 261 patients, ten different surgical techniques were used to repair penile urethral strictures. One-stage techniques were used in 129 (49.4%) cases, first stage in 98 (37.6%), and two-stage in 34 (13%). In 83 (31.8%) cases, the oral mucosa was used as the substitute material, and in 50 (19.1%) cases penile skin was used (35 free grafts and 15 pedicled flaps).

1. *First-stage urethroplasty* The technique was originally described by Johanson [11]. The diseased urethra (Supplementary Fig. 1) was fully opened, leaving a wide meatus proximally to void through. The patients don't accept any risk of stricture recurrence and refused the second-stage urethral reconstruction and remained with the new-meatus located at a different site from the balanic sulcus to the base of the penis, according to the stricture length (Supplementary Fig. 2).
2. *Meatotomy* The external urinary meatus and the navicularis urethra are fully opened ventrally, and the meatus is moved down in healthy urethral mucosa. Patients refused any further treatment, requiring for definitive surgical solution.
3. *Two-stage oral mucosa graft* This technique was used in patients who request the complete reconstruction of the urethral canal up to the tip of the glans. The urethra was opened at the first stage as described above (Supplementary Fig. 3A). After a median time of 6/9 months the second stage was performed. The urethral mucosal plate was longitudinally incised and the wings of the urethral plate were laterally mobilized to create a wide bed for the graft location (Supplementary Fig. 3B). The oral mucosal graft was fixed onto the bed of the dorsal urethrotomy using Glubran® glue

(Supplementary Fig. 3C, D, E). The penile skin margins are incised. and the urethra was tubularized up to the glans over Foley 12 F. grooved silicone catheter (Supplementary Fig. 3F, G). The penile skin is closed (Supplementary Fig. 3H).

4. *Meatoplasty* Meatoplasty was selected for young patients who do not accept, for aesthetic reason, a simple meatotomy. The external urinary meatus and the navicularis urethra are fully opened ventrally, and the meatus is again moved up to the glans using graft or flap transposition.
5. *One-stage oral mucosa graft* In non-obliterative stricture (Supplementary Fig. 4), we used the technique described by Asopa [6, 7]. The penile urethra was exposed by perineal incision (Supplementary Fig. 5A, B, C). The tract of the stricture was opened, and the urethral plate was longitudinally incised and the wings of the urethral plate were laterally mobilized to create a wide bed for graft location (Supplementary Fig. 5D). The oral mucosal graft was fixed onto the bed of the dorsal incision using Glubran® 2 (Supplementary Fig. 5E). The urethra was closed over Foley 12 F. grooved silicone catheter. The penis was stretched on his original position and perineal opening was sutured (Supplementary Fig. 5G, H).
6. *End-to-end anastomosis* The technique was used in selected cases with short penile strictures. To avoid post-operative penile chordee, two techniques were used:

   In short strictures, we performed longitudinal stricturotomy and transverse closure according to the Heinecke Mickulicz approach for stricturoplasty in intestinal surgery and as suggested by Mundy for bulbar non-transecting urethroplasty [12].

   In longer strictures, the penile urethra was approached by perineal incision and the bulbar urethra was fully mobilized to reach the penile urethra without tension according to the technique described by McGowan and Waterhouse in 1964 and later suggested by some authors for hypospadias repair [13–16].
7. *Two-stage urethroplasty* The urethra was fully opened at the first stage as described above (1). After a median time of 6/9 months, the second stage was performed. A wide neo-urethra strip was created consisting of the original mucosal urethral plate together with the adjacent penile skin that had been sutured to it. The neo-urethral plate was tubularized over the catheter from the abnormal meatus to the tip of the glans.
8. *One-stage penile skin flap urethroplasty* We used the modified Orandi's flap technique [17, 18] (Supplementary Fig. 6A, B). The urethra was dissected from the corpora cavernosa, rotated to expose the dorsal surface and opened (Supplementary Fig. 6C, D). A longitudinal island of penile skin was dissected based on the dartos fascial flap and moved over the corpora cavernosa (Supplementary Fig. 6E). A Foley 12 F. grooved silicone grooved catheter was inserted and the urethral plate was rotated over the skin island (Supplementary Fig. 6F). At the end of the procedure, the skin flap was completely covered by the urethra (Supplementary Fig. 6G), and the penile skin incision is sutured (Supplementary Fig. 6H).
9. *One-stage penile skin graft urethroplasty* The technique was the same as that described above (5). The urethral plate was augmented using a graft of penile skin harvested after circumcision.
10. *One-sided dorsal urethroplasty* We used the technique described in 2009 by Kulkarni et al. for the bulbar and pan-urethral stricture repair [19]. The penile urethra is longitudinally opened along its lateral surface, avoiding full dissection from the corpora cavernosa and the urethral lumen is enlarged by an oral graft.

Statistical analysis and description of risk calculator development

Descriptive statistics included frequencies and proportions for categorical variables. Medians, and interquartile ranges (IQR) were reported for continuously coded variables. Analyses consisted of several steps. First, univariable Cox regression models tested for predictors of treatment failure. Second, Kaplan–Meier curves were plotted to graphically explore the failure-free survival rates, according to univariable-identified predictors. Third, only statistically significant variables ($p < 0.05$), in univariable analysis, were entered into the multivariable analysis. Then, multivariable logistic regression model—for prediction of treatment failure—was constructed and its discrimination ability was tested with the Harrell's *C* index. Once the model was generated, it was used to develop the risk calculator, which took the form of an interactive Excel-sheet that accepts patient covariate information and returns an estimated probability percentage of treatment failure, based on the validated model. The risk-calculator was set to predict the risk of treatment failure at 10 years from surgery and it is available online, as supplementary material (Supplementary File 1). Analyses were performed using the R software environment for statistical computing and graphics.

Results

A total of 261 patients, with an average age of 55 years, comprised the study cohort. Patients and stricture features are fully reported in Table 1. Median stricture length was 3 cm. Out of 261 patients, 197 (75.5%) undergone

Table 1 General characteristics of the 261 patients with penile urethral stricture treated at our referral center

Variables	Overall (%)
BMI	
Median	26
IQR	23–28
Age	
< 50	107 (41)
≥ 50	154 (59)
Smoking	
Former	62 (23.8)
Current	71 (27.2)
Never	128 (49)
Diabetes	
No	242 (92.7)
Yes	19 (7.3)
Etiology	
Idiopathic	105 (40.2)
Catheter or other	80 (30.7)
Instrumentation	76 (29.1)
Length	
< 4	138 (52.9)
≥ 4	123 (47.1)
Previous treatment	
No	64 (24.5)
Yes	197 (75.5)
Techniques	
One-stage	129 (49.4)
First-stage	98 (37.5)
Two-stage	34 (13)
Use of graft	
None	128 (49)
Yes	133 (51)
Techniques	
First-stage urethroplasty/meatotomy/meatoplasty	107 (41)
End-to-end	7 (2.7)
Grafting/2-stages	147 (56.3)

previous treatments. Median follow-up was 108 months (IQR 60–161). Five techniques showed more than 10 years' follow-up, and five techniques ahowed lesser than 10 years (Table 2).

Out of 216 patients, 201 (77%) were classified as success and 60 (23%) as failures. The success rate according to the surgical technique is summarized in Table 2. The first-stage techniques provided 86.7% success rate, the two-stage 76.5%, and the one-stage 69.8%. Younger patients showed lesser success rate than the older counterparts. The success rate decreased in relation to stricture length: > 80% for short strictures, and < 70% for long strictures. Only patients who undergone previous failed associated treatments showed less success rate (< 70%) compared to patients who undergone a single treatment. Catheter-induced urethral strictures showed less success rate (< 70%) when compared to the other etiological-induced strictures. Skin flap (66.7%) showed similar success rate than skin graft techniques (65.7%). The oral mucosa was superior (71.4%) to penile skin (66%), as a substitute material. Only three techniques showed a success rate > 80%, 4 techniques > 70%, and three techniques < 70%. The surgical techniques with long follow-up had lower success rate (< 80%), and the majority of techniques (3 of 5) with short follow-up had higher success rate (> 80%). It is of interest that interaction test showed a statistically significant correlation between length of stricture (≥ 4 cm) and urethroplasty technique (two-stage or grafting), with $p = 0.014$. Conversely, no statistically significant interaction ($p = 0.42$) was found between length of stricture (≥ 4 cm) and the use of graft (both results not shown).

Predictors of treatment failure

Univariable and multivariable Cox regression models are presented in Table 3. Here, smoking habits ("former smoker", hazard ratio [HR] 2.12, 95% confidence interval [95% CI] 1.10–4.04, $p = 0.025$), etiology ("instrumentation", HR 2.55, 95% CI 1.31–4.96, $p = 0.006$) and use of graft for urethroplasty ("graft", HR 1.83, 95% CI 1.04–3.22, $p = 0.037$) were univariably associated with higher risk of treatment failure. After multivariable adjustment, only instrumentation (HR 2.91, 95% CI 1.32–6.41, $p = 0.008$) and former smoker (HR 2.10, 95% CI 1.01–4.36, $p = 0.047$) remained statistically significant. Figure 1 presented the Kaplan–Meier curves for failure-free survival. Again, "former smoker" ($p = 0.043$), "instrumentation", ($p = 0.018$) and "graft" ($p = 0.034$) were associated with lower failure-free survival rates. The *C* index of our multivariable model was 59%. According to our multivariable Cox regression-based risk calculator, the probability of treatment failure at 10 years ranged from 5.8% for patients with favorable characteristics (e.g. current smokers, no use of grafts and idiopathic etiology) to 41.1% for patients with unfavorable characteristics (e.g. former smokers, use of graft, and instrumentation etiology).

Discussion

Surgical treatment and related guidelines for management of penile urethral strictures still represents a challenging problem. Here, we aim to identify predictors of treatment failure after penile urethroplasty in a homogeneous large series of patients, also developing a dedicated risk calculator for patients who underwent penile urethroplasty that might be

Table 2 Success rate according to the surgical technique

N	Surgical technique	No. patient (%)	Median age (years)	Median stricture length (cm)	Median previous treatments	Success (%)	Failure (%)	Median follow-up (months)
1	First-stage urethroplasty	45 (17.2%)	60	3	1	41 (91.1%)	4 (8.9%)	78
2	Meatotomy	53 (20.3%)	53	1	1	44 (83%)	9 (17%)	101
3	Two-stage oral mucosa graft	20 (7.7%)	50	5	1	16 (80%)	4 (20%)	84
4	Meatoplasty	9 (3.4%)	42	2	1	7 (77.8%)	2 (22.2%)	151
5	One-stage oral mucosa graft	59 (22.6%)	61	4	2	43 (72.9%)	16 (27.1%)	78
6	End-to-end anastomosis	7 (2.7%)	60	2	1	5 (71.4%)	2 (28.6%)	209
7	Two-stage urethroplasty	14 (5.4%)	45	4	1	10 (71.4%)	4 (28.6%)	146
8	One-stage penile skin flap urethroplasty	15 (5.7%)	56	4	2	10 (66.7%)	5 (33.3%)	157
9	One-stage penile skin graft urethroplasty	35 (13.4%)	48	4	1	23 (65.7%)	12 (34.3%)	156
10	One-sided dorsal urethroplasty	4 (1.6%)	56	5	2	2 (50%)	2 (50%)	113
	Total	261	55	3	1	201 (77%)	60 (23%)	114

Table 3 Univariable and multivariable Cox regression models predicting treatment failure in the overall population (261 pts)

Variables	Univariate table				Multivariate table			
	HR	2.50%	97.50%	*p*	HR	2.50%	97.50%	*p*
Age (≥ 50 years)	1.09	0.64	1.86	0.7	0.80	0.41	1.57	0.5
BMI (kg/m^2)	1.02	0.94	1.11	0.5	0.98	0.89	1.08	0.6
Never smoked (Ref.)								
Current smoker	0.94	0.51	1.74	0.8	0.82	0.43	1.58	0.5
Former smoker	2.12	1.10	4.08	0.025	2.10	1.01	4.36	0.047
No diabetes (ref.)								
Diabetes	1.48	0.46	4.79	0.5	1.36	0.39	4.70	0.6
Etiology idiopathic (Ref.)								
Catheter or other	1.76	0.93	3.32	0.08	1.43	0.70	2.93	0.3
Instrumentation	2.55	1.31	4.96	0.006	2.91	1.32	6.41	0.008
Stricture length (< 4 cm) Ref								
Stricture length (≥ 4 cm)	1.36	0.80	2.30	0.2	0.74	0.39	1.42	0.3
No previous treatment (Ref.)								
Previous treatment	1.17	0.57	2.40	0.6	0.80	0.38	1.72	0.5
One-stage (Ref.)								
First-stage	0.60	0.31	1.15	0.1	1.94	0.39	9.77	0.4
Two-stage	1.16	0.54	2.51	0.7	1.21	0.40	3.62	0.7
No use of graft (Ref)								
Use of graft	1.83	1.04	3.22	0.037	1.01	0.25	4.15	0.9
First-stage urethroplasty/meatotomy/meatoplasty (Ref.)								
End-to-end	0.99	0.22	4.51	0.9	1.10	0.14	8.93	0.9
Grafting/2-stages	2.13	1.11	4.08	0.023	3.73	0.45	31.09	0.2

used to counsel patients according to their pre-operative risk of failure. Our study reached several noteworthy findings.

Firstly, urethral instrumentation showed to be an independent predictor in our large retrospective cohort. Basically, etiology of penile urethral stricture is mainly related to FHR and LS [20–22]. In our survey, excluding FHR and LS, we thought catheter and instrumentation as the most frequent etiology of penile stricture. Unexpectedly, we found that the majority of our patients (40.3%) showed idiopathic strictures, like in the bulbar urethra [20–22]. Minor unrecognized perineal trauma in pediatric age is suggested as true etiology of idiopathic urethral strictures in the bulbar tract [20–22]. But, it is difficult to suppose the same hypothesis for the penile tract also. More epidemiologic studies would

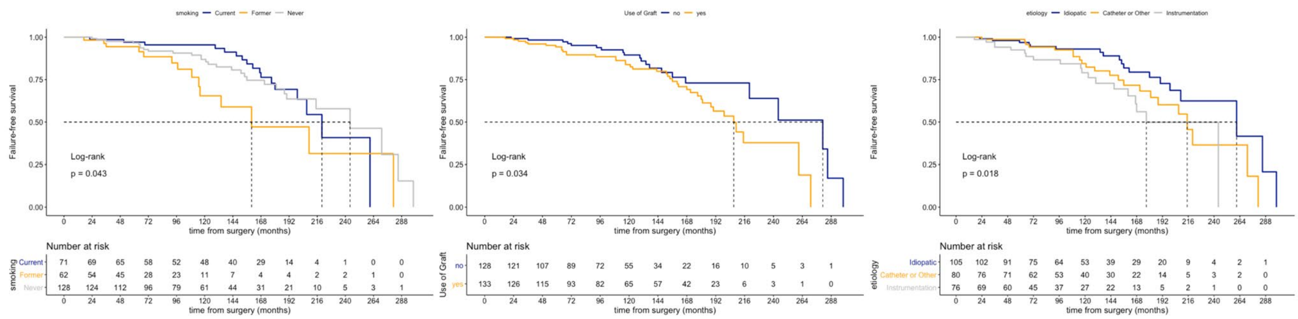

Fig. 1 Right: Kaplan–Meier curve depicting failure-free survival rate according to the etiology of the stricture Middle: Kaplan–Meier curve depicting failure-free survival rate according to the use of grafts. Left: Kaplan–Meier curve depicting failure-free survival rate according to the patient's smoking habits

be necessary to better clarify the etiology of these idiopathic penile urethral strictures.

Secondly, previous failed treatments of the stricture did not impact the outcome. Similar result was found in 1998, when Armenakas et al. reported, in a series of 19 meatus and navicularis strictures, that previous multiple dilations did not influence the success rate of urethroplasty [23]. Interestingly, in our experience, patients who undergone previous failed associated treatments (urethrotomy/urethroplasty plus periodic dilation) showed less success rate (<70%) compared to patients who undergone a single dilation, urethrotomy, or urethroplasty. Consequently, further studies should investigate whether the number of previous procedures might be an independent factors of treatment failure, instead of single and isolated previous procedures.

Thirdly, the length of stricture was not statistically associated with the rate of treatment failure either in univariable or in multivariable analyses. Such might be a consequence of the heterogeneity of our patient population, where different surgical techniques were employed according to the length of the stenosis. Indeed, when the stenosis was short (less than 4 cm), we typically adopted an end-to-end, single-stage, meatotomy or meatoplasty approaches. Conversely, in longer stenosis (≥ 4 cm), the two-stage or grafting techniques were preferred. This correlation is also visible in our analyses, where the interaction test between the length of stenosis (≥ 4 cm) and the surgical techniques (two-stage or grafting) comes statistically significant ($p = 0.014$). Taken together, we can postulate that the stricture length influenced the treatment decision making towards one or the other surgical techniques, thus length of stenosis cannot be considered independent to the outcome. In contrary, the length of stenosis can be associated with treatment outcome when only a homogeneous surgical series—similar surgical technique for all patients—is considered, as it is not the case of the current study.

Thirdly, the type of graft used for urethral reconstruction showed to be crucial for treatment outcome. The oral mucosa showed to be greatly superior to the penile skin as substitute material: 72.9% vs 65.7% in one-stage techniques, and 80% vs 71.4% in two-stage techniques. Moreover, the use of any grafts was associated with higher risk of failure, compared to no use of grafts, according to our Cox regression analysis (HR 1.83). The latter may reflect once again that longer strictures, which required the use of substitutive material, were intrinsically associated with higher risk of failure. Thus, the use of graft was also indirectly associated with higher treatment failure. However, such association was not support by our analyses, where no statistically significant interaction was identified between use of graft and stricture length ($p = 0.42$). Taken together, we can postulate that the use of graft represents by itself an intrinsic risk factor for treatment failure due to the different biological behavior of the graft (oral mucosa or prepuce skin) compared with normal urethral mucosa. Such, should be kept in mind every time we offer a surgical solution that requires the employment of substitutive graft material, by the fact that such increases the risk of treatment failure. This aspect is also noteworthy, especially in the context of the regenerative and engineered surgery for urethroplasty, which is growing in these recent years [24, 25].

Our study is not without limitations. First and foremost, our model showed limited discrimination ability with a *C* index not reaching 60%. Such could be the results of intrinsic limitation of the current series. Although our survey included a relatively large series of homogeneous patients, some subgroups included a small series of patients and thus the results may not be fully sufficient to draw definitive conclusions. More studies including a larger series of patients are welcomed to better clarify some of our preliminary viewpoints. Moreover, further series of patients are also welcome to externally validate our model, which is a crucial step for confuting its value. Finally, the absence of quality of life questionnaires or patient-reported outcome measures is another great limitation of our study, above all when we are investigating the outcome of penile urethra reconstruction which involves not only functional, but also aesthetic and sexual aspects.

Conclusions

To repair penile strictures, the surgeon should be confident with many different surgical options in one- or staged-repair. The appropriate selection of the technique remains challenging and based not only on stricture features, but mainly on surgeon background and preference. In this context, the availability of a risk calculator for predicting the risk of treatment failure might be useful for counseling patients and for treatment decision-making. Indeed, we saw that the etiology of the strictures, the use of grafts, and also the patient's smoking habits are influencing the treatment outcome, at long-term.

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Compliance with ethical standards

Conflict of interest This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. None conflict of interest.

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