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Development of a prediction model for postoperative complications after primary hypospadias correction☆

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ABSTRACT

Purpose: To develop a prediction model for postoperative complications after primary one-stage hypospadias correction to improve preoperative parental counseling.
Materials and methods: In this retrospective cohort study, data were collected from 356 patients with anterior or middle hypospadias who had a one-stage hypospadias correction from 2003 onwards. Potential treatment- and patient-related factors were selected and used to develop a prediction model for postoperative complications within one year (wound-related complications, urinary tract infections, fistulas, stenosis, and prepuce-related complications). Multivariable logistic regression analysis with stepwise backward selection and a *p*-value of 0.20 was used to select the final model, which was internally validated using the bootstrap procedure.
Results: Complications within one year postoperatively occurred in 66 patients (19%), of which 13% and 37% were seen in anterior and middle type of hypospadias, respectively. Hypospadias phenotype, surgical technique, chordectomy, and surgeon's experience were included in the final prediction model, whereas none of the patient-related factors were. The final model had a good discriminative ability (bias corrected C statistic 0.70) and calibration.
Conclusion: Using easily obtainable information, this model showed good accuracy in predicting complications within one year after hypospadias surgery. It is a first step towards individualized risk prediction of postoperative complications for anterior and middle hypospadias and can assist in preoperative parental counseling.
Type of study: Prognostic study.
Level of evidence: Level II.

Hypospadias is a congenital malformation in boys with estimated prevalence in Europe ranging between 1.7 and 3.8 per 1000 live births [1,2]. Surgical treatment of hypospadias is usually performed within the first or second year of life [3]. Although surgical correction is indicated in most patients [1], this is usually an elective procedure with long-term complication rates as high as 50% [4]. After hypospadias surgery, approximately half of the parents experience decisional regret, with postoperative complications as risk factor for regret according to Lorenzo et al., but not according to Ghidini et al, [5,6]. An objective perspective of the complication risk may improve preoperative parental counseling and help parents make better informed decisions on whether or not they will have their son operated upon.

Several studies tried to identify risk factors for the development of complications and most agree that hypospadias phenotype (e.g. anterior, middle, or posterior), preoperative existence of chordee (for which surgery is indicated), surgeon's experience, and surgical technique influence number complications [7–11]. However, the risk factors identified have never before been combined in a prediction model.

Although treatment-related factors were investigated most frequently, factors concerning the neonatal period, such as mode of delivery and breast feeding, and other patient-related factors, such as exposure to smoking in the first years of the child's life, may also play an important role. The effects of these factors on the child's general health or immune status [12–14] may influence the risk of postoperative complications. Some factors were studied in association with surgical complications before [12,14], but never for patients with hypospadias. The aim of this study was to develop and internally validate a prediction model using treatment- and patient-related factors to predict the risk of postoperative complications within one year after primary hypospadias correction. This prediction model may help physicians with preoperative parental counseling.

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1. Materials and methods

1.1. Study population

In this retrospective cohort study, patients were derived from AGORA (Aetiologic research into Genetic and Occupational/ environmental Risk factors for Anomalies in children), a large ongoing data- and biobank coordinated by the Radboud university medical center (Radboudumc), the Netherlands, including diagnostic and questionnaire data and DNA samples from children with congenital malformations and their parents. Routine patient recruitment for AGORA started in 2004, and details about this are described elsewhere [15]. Patients who had primary hypospadias correction in the Radboudumc were selected for this study. Patients were excluded when medical records contained insufficient information, preoperative meatal location was posterior or unknown, or surgery was performed as multistage correction or before 2003. Follow-up of less than one year after initial hypospadias correction was also reason for exclusion unless a complication occurred within the first year.

1.2. Data collection

At inclusion in the AGORA data- and biobank, the patients' parents were asked to complete the AGORA questionnaire concerning demographics, lifestyle before, during, and after pregnancy, and pregnancy outcome. Relevant clinical information, treatment characteristics, and postoperative outcome were obtained from medical records by a medical doctor (ED) supported by medically trained research assistants using structured data forms, which was carried out in 2015. Between April and August 2015, parents were invited to complete an online questionnaire concerning the neonatal period and the patient's health and exposures in the first two years of life.

Ethical approval was granted by the Regional Committee on Research involving Human Subjects. All parents gave written informed consent for the study.

1.3. Definitions of outcome and prognostic variables

We used the occurrence of postoperative complications within one year after initial hypospadias surgery as described in the medical records as outcome variable. There is a follow-up at the outpatient clinic after one week, six weeks, and six and twelve months. Hypospadias-related complications were described as wound-related complications (wound dehiscence, wound infection, or meatal retraction), urinary tract infections (UTIs), urethrocutaneous fistulas, meatal or urethral stenosis, and prepuce-related complications (prepuce fistulas, prepuce dehiscence, or phimosis). For patients who needed reintervention within one year after initial surgery ($n = 29$, 8%), only complications after the initial repair were analyzed.

We selected potential prognostic variables based on importance according to the literature. Because we aimed to develop a model that could be used for preoperative risk prediction, only variables available during preoperative parental consultation were selected. The definition and categories of all variables taken into consideration for the prognostic model can be found in Table 1.

1.4. Statistical analysis

Descriptive statistics were used to provide an overview of all relevant variables and to perform a nonresponse analysis for the online parental questionnaire. Method of anesthesia, perioperative use of antibiotics, and type of postoperative bandage were excluded as prognostic variables because of little variation among current patients owing to the present-day standard of care. Eleven candidate prognostic factors remained for modeling of which five were treatment-related (hypospadias phenotype, type of surgery, surgeon's experience, chordectomy, and type of prepuce reconstruction) and six patient-related (birth weight, mode of delivery, breast feeding, child age and weight-for-age at time of surgery, and exposure to smoking in the first two years of life).

Missing values were imputed with 50 data replicates using multiple imputation by the chained equations (MICE) method [16], in which all prognostic variables were considered and the outcome variable (postoperative complications) were taken into account. Using multivariable logistic regression and stepwise backward selection (with individual variable p-values of 0.20), variables were selected for the final model. The p-values were derived from the significance of the pooled estimate for that variable obtained from the imputed datasets. Estimates were pooled using Rubin's rule [17].

1.5. Model performance and validation

The model's performance was examined with discrimination and calibration statistics [18]. Discrimination was assessed by the C statistic, also known as the area under the receiver operating characteristic (ROC) curve (AUC) and calibration by the Hosmer–Lemeshow test. To provide a more accurate estimate of model performance, 1000 random bootstrap samples were drawn from each imputed data set to obtain a corrected C statistic for each set [19]. The mean of these corrected C statistics was used to indicate model discrimination. Compared to other methods of internal validation, such as split-sample and cross-validation modeling, bootstrap resampling techniques produce stable and nearly unbiased estimates of predictive accuracy with better efficiency [19].

All statistical analyses were performed using SPSS Statistics, Version 22.0 for Windows (IBM SPSS Inc., Chicago, IL, USA) and RStudio version 1.0.143 (RStudio: Integrated Development for R. RStudio, Boston, MA, USA http://www.rstudio.com/).

2. Results

2.1. Study population

Of the 945 hypospadias patients available in the AGORA data- and biobank (Fig. 1), 589 patients were excluded, mostly because of surgery before 2003 ($n = 308$), insufficient medical information ($n = 86$), proximal hypospadias ($n = 54$), or multistage correction ($n = 43$), leaving 356 patients for analysis. The online parental questionnaire was completed for 235 patients (66%). Nonresponse analysis showed that sons of responders more often had prepuce reconstruction and a higher birth weight than those of nonresponders (65% vs 52%, and 3400 g vs 3135 g, respectively).

The majority of patients were of Caucasian origin and the median follow-up after hypospadias correction was 3.2 years (5–95% range: 1.2–8.9 years). The preoperative meatal location was anterior in 77% and middle in 23% of patients (Table 2). Anterior hypospadias was most frequently corrected using MAGPI / meatoplasty / meatal or urethral advancement (57%), whereas TIP / tubularization was most common for middle hypospadias (63%). A chordectomy was performed in 66% of patients, prepuce reconstruction in 61%, and circumcision in 34%. The prepuce was left untouched in 5% of patients on specific request of the parents. Ninety percent of corrections were performed by one of the three current pediatric urologists. The median surgeons' experience was 9.9 (0.9–17.7) years.

Median birth weight was 3330 (1978–4262) g and 22% of the children were born by caesarean section. Seventy-seven percent of children were breast fed, with a median duration of 4.0 (0.2–11.2) months. Median age at time of surgery was 13.5 months (9.8 months–5.0 years). Approximately 27% of patients were exposed to smoking in the first two years of life.

Table 1
Definitions and categories of treatment and patient-related factors.

Treatment-related factors Name and categories	**Definition**
Hypospadias phenotype	*Original meatal location*
- Anterior	Hypospadias sine hypospadias (all types of hypospadias in which there was a prepuce deformity and/or penile curvature for which a chordectomy was performed), glanular, and (sub)coronal forms of hypospadias
- Middle	Distal penile, midshaft, or proximal penile forms of hypospadias
Surgical technique	*The type of surgery used for the primary hypospadias correction*
- No urethroplasty	Prepuce reconstruction or circumcision and/or correction of penile curvature without urethral reconstruction
- TIP / Tubularization	Tubularization using tubularized incised plate urethroplasty (TIP) or another type of tubularization plasty
- MAGPI / meatusplasty and urethral or meatal advancement	Meatal advancement with glansplasty incorporated (MAGPI), meatoplasty, or meatal or urethral advancement
- Prepuce flaps	Preputial flaps, such as onlay flap, Duckett, or double faced island flap
- Mathieu and other techniques	Mathieu technique or other types of surgical techniques used
Chordectomy	
- Yes	Correction of a penile curvature, regardless of the type of correction
- No	No correction of penile curvature indicated or performed
Prepuce surgery	
- Prepuce reconstruction	Reconstruction of the prepuce
- Circumcision	Circumcision of the prepuce
- No reconstruction performed	No reconstruction or circumcision of the prepuce was indicated or performed
Surgeon's experience	*Years of experience of the surgeon since independently performing hypospadias corrections (continuous variable)*
Method of anesthesia	
- General anesthetics with caudal or penile block	Additional to general anesthetics, a caudal or penile block was administered
- General anesthetics only	Additional to general anesthetics no additional block was administered
Perioperative use of antibiotics	
- Yes	Antibiotics (any type) were administered during perioperative care
- No	No antibiotics were administered perioperative care
Type of postoperative bandage	
- Tegaderm	Postoperative application of tegaderm
- Foam	Postoperative application of foam
- No or light bandaging	Postoperative application of no or a light bandage
Patient-related factors Name and categories	
Birth weight	*Birth weight in grams (continuous variable)*
Mode of delivery	
- Natural birth	Child was delivered with a natural birth
- Caesarean section	Child was delivered with a caesarean section
Breast feeding	
- Any breastfeeding	Child received breast feeding, regardless of duration
- No breast feeding	Child did not receive any breast feeding
Child age at time of surgery	
- <18 months	Child was younger than 18 months
- ≥18 months	Child was aged 18 months or older
Weight-for-age at time of surgery	*Weight at time of surgery was used to calculate weight-for-age z-scores using WHO Child Growth Standards* [29]
Exposure to smoking during the first 2 years of life	
- Exposure to smoking	Any exposure to smoking in the household or vicinity of the child
- No exposure	No exposure to smoking in the household or vicinity of the child

2.2. Prediction model

One or more hypospadias-related complications within one year after initial one-stage hypospadias repair were found in 66 patients (19%), of which 45 patients had a reintervention. Wound-related complications were the most frequent ($n = 40$). Fistulas ($n = 11$), UTIs ($n = 8$), stenosis ($n = 4$), and prepuce-related complications ($n = 14$) occurred in 1%–4% of patients.

A number of patients had missing information on prognostic variables mostly owing to incomplete online questionnaires: chordectomy ($n = 2$, <1%), prepuce surgery ($n = 4$; 1%), surgeon's experience ($n = 3$; <1%), birth weight ($n = 23$; 6%), mode of delivery ($n = 182$; 51%), breast feeding ($n = 125$; 35%), weight-for-age at time of surgery ($n = 19$; 5%), and exposure to smoking ($n = 130$; 37%). By multiple imputation of these missing values, however, the total study population could be used in development of the prediction model.

In the final model, no patient-related variables remained, but the treatment-related variables hypospadias phenotype, surgical technique (no urethroplasty vs. others and MAGPI / meatusplasty and meatal or urethral advancement vs. others), chordectomy, and surgeon's experience were included. These variables are presented in Table 3, with their β coefficient estimates and standard errors and the corresponding odds ratios (ORs) with 95% confidence intervals (CIs). Performing no urethroplasty or performing a MAGPI / meatusplasty and meatal or urethral advancement instead of another surgical technique seemed to decrease the risk of postoperative complications, whereas having a middle hypospadias, chordectomy, and more years of surgical experience was associated with increased complication risks.

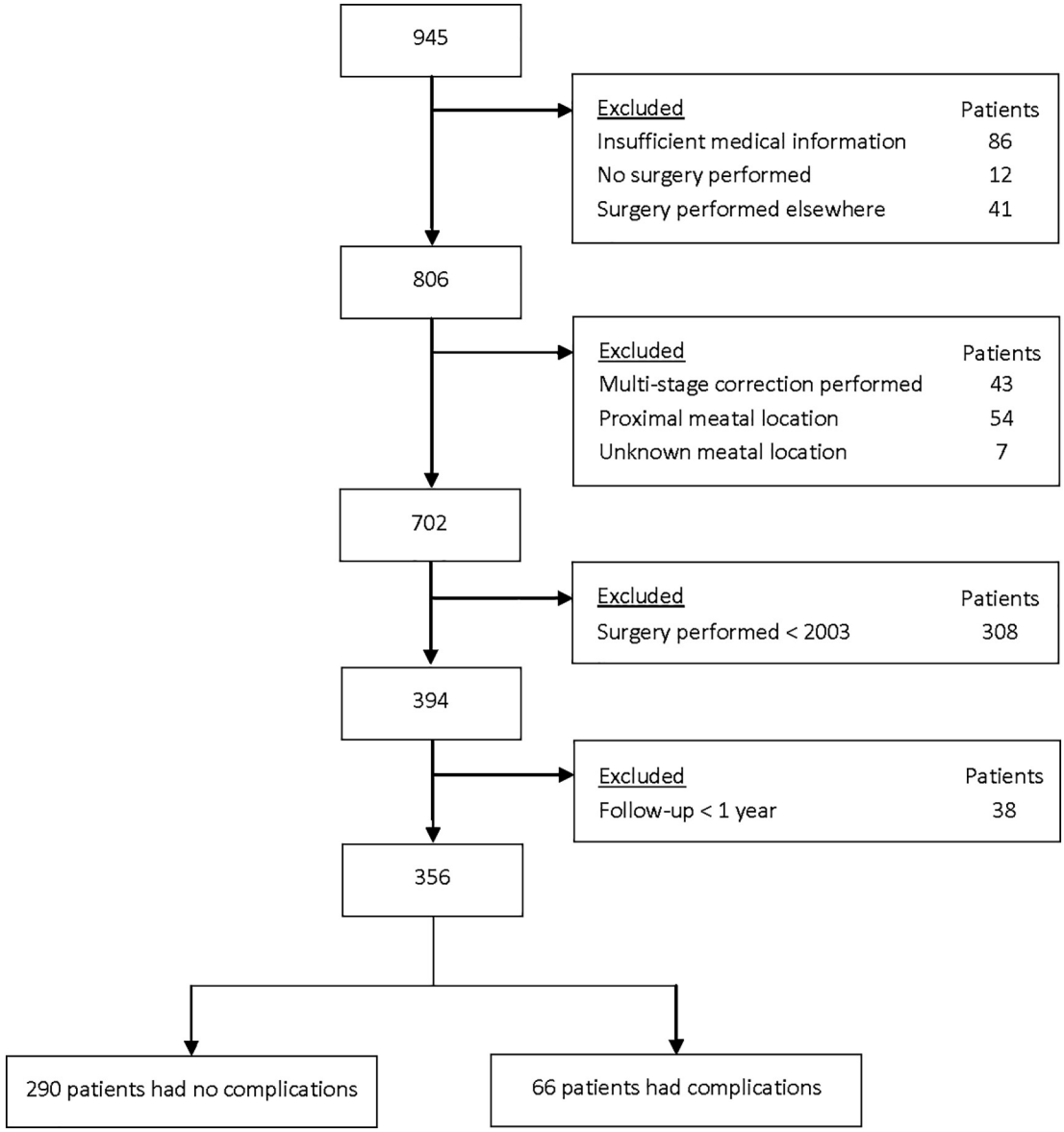

Fig. 1. Flowchart of selection and exclusion of patients.

By inserting the type of hypospadias and the relevant treatment information for a patient in the logistic regression model with the coefficients from Table 3, probability estimates can be calculated for the individual patient's postoperative complication risk. The model demonstrated good discrimination (C statistic = 0.76; bias-corrected C statistic = 0.70) and calibration, as no substantial deviation from the 45° line of perfect fit was observed (Hosmer–Lemeshow test $\chi^2 = 5.9$; $p = 0.66$) (Fig. 2).

3. Discussion

This is the first study to develop and internally validate a prediction model for the risk of postoperative complications after hypospadias surgery. Hypospadias phenotype, surgical technique, chordectomy, and surgeon's experience were found to be prognostic factors and the model had a good discriminative ability and calibration. The model may improve preoperative counseling by giving parents an estimate of the postoperative complication risk.

3.1. Strengths and limitations

The strengths of this study are the extensive (partially routine) data collection and the availability of a relatively large number of patients who had hypospadias surgery in one clinic. Therefore, many variables could be included in the initial prediction model, including various patient-related factors, and be assessed for their effects on postoperative complications. A limitation of the study is the retrospective nature of the data. Although medical records were reviewed to gather information on treatment-related factors and complications, these were not always reported in a standardized manner and were based on the clinical opinion of the evaluating physician or nurse practitioner. As observed in previous studies, complication registration in medical records may be incomplete [20,21], which could have reduced the accuracy of the model.

Most patient-related factors were collected using self-reported questionnaires, sometimes completed a long time after the time period of interest. This may have introduced some misclassification, but except

Table 2
Characteristics of the total study population and divided by the occurrence of main complications within 1 year after hypospadias repair.

	Total[a]		No complications		Complications within 1 year[b]	
	$n = 356$		$n = 290$		$n = 66$	
	n	(%)	*n*	(%)	*n*	(%)
Treatment-related factors						
Hypospadias phenotype						
Anterior	274	(77.0)	238	(82.1)	36	(54.5)
Middle	82	(23.0)	52	(17.9)	30	(45.5)
Surgical technique						
No urethroplasty[c]	53	(14.9)	45	(15.5)	8	(12.1)
TIP / Tubularization[d]	99	(27.8)	68	(23.4)	31	(47.0)
MAGPI / meatusplasty and meatal or urethral advancement[e]	172	(48.3)	157	(54.1)	15	(22.7)
Prepuce flaps[f]	20	(5.6)	11	(3.8)	9	(13.6)
Mathieu and other techniques	12	(3.4)	9	(3.1)	3	(4.5)
Chordectomy						
Yes	233	(65.8)	178	(61.8)	55	(83.3)
No	121	(34.2)	110	(38.2)	11	(16.7)
Prepuce surgery						
Prepuce reconstruction	213	(60.5)	181	(63.3)	32	(48.5)
Circumcision	120	(34.1)	89	(31.1)	31	(47.0)
No reconstruction performed	19	(5.4)	16	(5.6)	3	(4.5)
Surgeon's experience in years, median (90% range)	9.9 (0.9–17.7)		9.6 (0.8–17.4)		11.4 (1.0–19.3)	
Patient-related factors						
Birth weight in grams, median (90% range)	3330 (1978–4262)		3340 (1997–4285)		3280 (1515–4280)	
Mode of delivery						
Natural birth	136	(78.2)	112	(77.8)	24	(80.0)
Caesarean section	38	(21.8)	32	(22.2)	6	(20.0)
Breastfeeding						
Yes	178	(77.1)	146	(77.7)	32	(74.4)
No	53	(22.9)	42	(22.3)	11	(25.6)
Child age at time of surgery						
<18 months	273	(76.7)	221	(76.2)	52	(78.8)
≥18 months	83	(23.3)	69	(23.8)	14	(21.2)
Weight-for-age at time of surgery as z-score, mean (SD)	−0.18 (1.19)		−0.16 (1.2)		−0.29 (1.15)	
Exposure to smoking in the first two years of life[g]						
Yes	61	(27.0)	49	(26.3)	12	(30.0)
No	165	(73.0)	137	(73.7)	28	(70.0)

[a] Numbers do not add up to total owing to missing values.
[b] Main complications are wound problems, urinary tract infections, fistulas, stenosis, and prepuce-related complications. The total number of these complications exceeds the number of main complications since patients can have multiple complications.
[c] The group 'No urethroplasty' entailed patients in which preputial reconstruction or circumcision and / or correction of the penile curvature were performed, but no urethral reconstruction.
[d] Tubularization using the tubularized incised plate urethroplasty (TIP) or another type of tubularization plasty.
[e] Meatal advancement with glansplasty incorporated (MAGPI).
[f] The group 'Preputial flaps' contained patients in which corrections, such as onlay flap, Duckett, or double faced onlay flap were performed.
[g] Exposure to smoking in the household or vicinity of the child.

for smoking, these variables (i.e. birth weight, mode of delivery, and breast feeding) were clearly defined and easy to recall, especially since birth of a child is a major life event. Owing to nonresponse and incomplete parental questionnaires, however, some patient-related variables contained a large number of missing values. This was remedied by multiple imputation, assuming that missingness was completely at random, although nonresponse analysis showed some differences between the responders (66%) and nonresponders (34%) in birth weight and prepuce surgery. As these factors were not included in the final prediction model, we expect these differences not to have had large consequences. To have a suitable number of events per variable for the development of the multivariable prediction model, the number of potential prognostic factors was reduced by excluding factors that have little variation in present-day standard of care [22].

Table 3
Variables included in the final prediction model with regression coefficient, standard error, adjusted odds ratio and 95% confidence interval.

Variables	β coefficient	Standard error	Adjusted odds ratio	95% Confidence interval
Intercept	−1.65	0.41		
Middle hypospadias	0.56	0.35	1.75	0.88–3.49
Surgical technique				
No urethroplasty[a]	−0.78	0.48	0.46	0.18-1.18
MAGPI / meatusplasty and meatal or urethral advancement[b]	−1.38	0.38	0.25	0.12–0.53
Chordectomy performed	0.80	0.37	2.23	1.07–4.62
Surgeon's experience[c]	0.39	0.16	1.48	1.08–2.01

[a] The patients in this group had prepuce reconstruction or circumcision and/or correction of the penile curvature without urethral reconstruction.
[b] Meatal advancement with glansplasty incorporated (MAGPI).
[c] Additional risk for every additional year of experience.

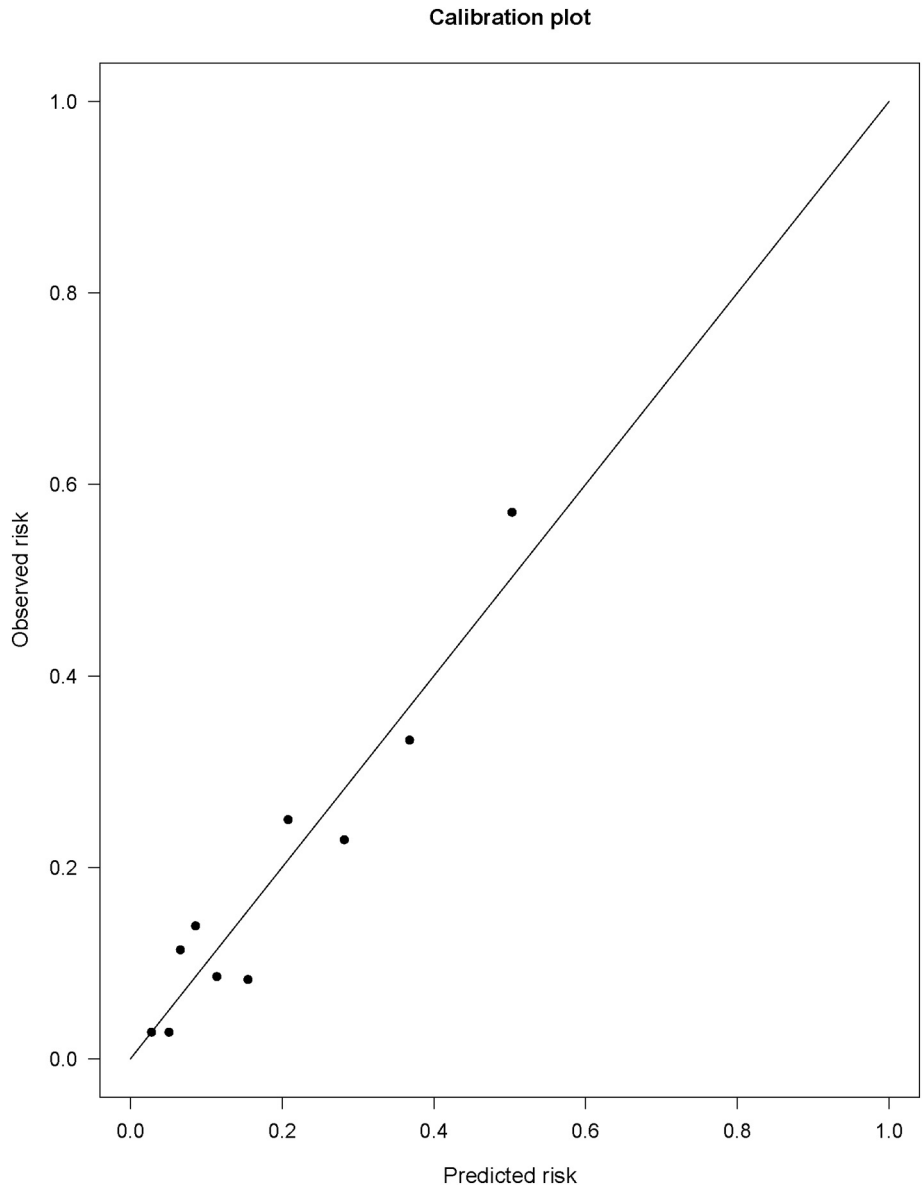

Fig. 2. Calibration plot.

3.2. Our findings in light of existing literature

Many studies have tried to identify factors influencing complication risk after hypospadias surgery, mostly focusing on treatment-related factors [7–11,23,24]. Although we expected patient-related factors to contribute to this risk as well, these factors were dropped from the prediction model in our analyses. The study showed that treatment-related factors (hypospadias phenotype, surgical technique, chordectomy, and surgeon's experience) indeed play an important role in the risk of complications. The model presented is the first to combine these treatment-related factors to predict the individual risk. Middle hypospadias phenotype and the need for a chordectomy resulted in higher complication risks which correspond with findings in previous studies, as are the results that certain surgical techniques have a lower risk than others [7,8,10,24]. However, whereas other studies showed improved results with more years of surgical experience [7,9], more experience seemed to have the opposite effect in our model. This is most likely because of the more experienced surgeons performing surgery on the more complicated cases in our hospital. Therefore, years of surgical experience should be considered as a proxy variable for one or more underlying treatment-related factors. Moreover, the results of the separate variables in the model are not strictly to be seen individually, but only in the view of the entire model. Although we took many variables into account in development of the model, several other variables may play a role in decision making around hypospadias surgery, which leave room for improvement of our model.

3.3. Clinical implications

Ideally, we would have developed a prediction model to optimize surgical circumstances, for example determining the type or timing of surgery with the lowest risk of complications. However, this was not possible with the observational data available for model development [25]. Our model was based on primary one-stage corrections for anterior or middle hypospadias performed in a university hospital. For posterior hypospadias, multistage corrections are mostly used, which have a higher complication rate [26]. Since reoperations have different

complication rates as well [27,28], this prediction model should not be used to predict complications after multistage corrections or repeat surgery.

Patients in our hospital are usually discharged after one overnight stay with a urethral dripping catheter in place. A nurse practitioner contacts the parents a few days later to ask for complications, and the patient visits the outpatient clinic one week after surgery to remove the postoperative dressing and urethral catheter. Medical care applied and postoperative follow-up may vary between medical institutions, potentially resulting in different reported complications rates. Therefore, external validation is advised before introducing this model in another hospital setting.

Because hypospadias correction is not required in all patients, it is important to provide parents with an objective perspective of the expected postoperative outcome and the complication risk during preoperative consultation, to help them make a well-informed decision. Our prediction model can inform and prepare parents regarding the development of complications, which will hopefully reduce decisional regrets afterwards.

4. Conclusion

To our knowledge, this study is the first to develop and internally validate a prediction model for complication risk after one-stage surgery for anterior and middle hypospadias. The final model included the factors hypospadias phenotype, surgical technique, chordectomy, and surgeon's experience and showed a good discriminative ability and calibration. We found patient-related factors not to predict postoperative complication risk. Although external validation is still needed, this model is a first step towards an effective individualized risk prediction of complications after hypospadias surgery and may improve preoperative parental counseling.

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