Original Article

A prediction model for risk factors of testicular atrophy after orchiopexy in children with undescended testis

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Background: There have been limited studies with small sample sizes about risk factors of testicular atrophy. Thus, we aimed to investigate the risk factors for testicular atrophy after orchiopexy in male children with undescended testes and develop a prediction model based on clinical variables.

Methods: We performed a retrospective review of data on children who underwent orchiopexy for undescended testes from 2013 to 2017. The variables assessed included age, laterality, testicular location, preoperative testicular volume ratio, deferens and epididymis anomaly, hormonal treatment, comorbidities, type of surgical procedure, operating time, and complications as the outcome of testicular atrophy. A nomogram was constructed to predict the probability of testicular atrophy. We also validated our model based on a prospective cohort of patients who underwent orchiopexy from January 2018 to December 2018.

Results: A total of 1,608 patients undergoing orchiopexy were included in the training cohort. The median age was 2.8 years (range, 0.5–11.3 years). After follow-up for 12 to 18 months (median, 14 months), 228 (14.2%) cases of atrophic testes were recorded. The independent predictors of testicular atrophy were preoperative testicular volume ratio [odds ratio (OR) 0.001, P=0.001], testicular location (OR 1.903, P=0.001), deferens and epididymis anomaly (OR 6.470, P=0.001), and two-stage Fowler-Stephens orchiopexy (OR 2.613, P=0.04). Successful validation was achieved, and a receiver operating characteristic (ROC) curve was constructed. The sensitivity and specificity of the prediction model were 78.1% and 77.5%, respectively. The area under the ROC curve was 0.851.

Conclusions: In patients with undescended testes, excluding those with chromosomal abnormalities and testicular nubbin, the incidence of testicular atrophy after orchiopexy is higher in patients with a lower testicular volume ratio, higher testicular location, deferens and epididymis anomaly, and in two-stage Fowler-Stephens orchiopexy. Therefore, this prediction model provides useful evidence for surgeons to choose an appropriate surgical procedure for undescended testes and predict the probability of testicular atrophy.

Keywords: Orchiopexy; testicular atrophy (TA); undescended testis (UDT); risk factors; prediction model

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Introduction

Undescended testis (UDT) is one of the most common congenital abnormalities in male neonates, affecting 1.0–4.6% of full-term and 1.1–45% of preterm neonates. After spontaneous descent within the six months of life, the incidence rate of UDT is 1% in full-term male infants at 1 year of age (1,2). Retractile testis doesn't need treatment as most of them will become normal, but it should be monitored carefully (3). Hormonal therapy for UDT is not recommended due to a low success rate of 20% (4). The universally accepted treatment is orchiopexy and the surgery should be finished before 18 months, according to European Association of Urology (EAU) guidelines and American Urological Association (AUA) guidelines (5). However, testicular atrophy (TA), which affects testicular function and fertility, can be a severe complication of orchiopexy. The incidence of TA in the literature ranges from 8% to 32% (6,7).

Although there have been a few reports on the risk factors for TA, their conclusions are insufficient. Stec *et al.* studied the factors influencing successful orchiopexy in 156 children and confirmed that the surgical procedure was associated with TA (8). Ein *et al.* retrospectively studied 1,400 children undergoing orchiopexy and concluded that the most significant risk factors associated with TA were high testicle, vas problems, and preoperative torsion (9).

To tackle the paucity of data due to few studies on this topic, and with issues such as small sample sizes and the lack of prediction models in previous studies (9,10), we composed the following research question: Which factors predispose to TA after orchiopexy and how do we predict this complication? We hypothesized that TA could be influenced by age, preoperative testicular volume (TV), testicular location, and the type of surgical procedure. We tested this hypothesis both retrospectively and prospectively, and developed a prediction model which included age, laterality, testicular location, preoperative TV ratio, deferens and epididymis anomaly, hormonal treatment, comorbidities, the type of surgical procedure and complications as variables. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-473).

Methods

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of Shenzhen Children's Hospital (2019007). It is an observation study, and the data are anonymous, so the informed consent was waived.

Study design

Our study had sequential phases of training and validation. For the training cohort, we searched the hospital information system for pediatric patients (age <14 years) with UDT from January 1st, 2013 to December 31st, 2017. Data were obtained from the hospital patient records and subsequent clinic visits. Patients were included if they underwent orchiopexy with a preoperative ultrasound test, were followed up for more than 1 year with an ultrasound scan, and if complete patient records were available. The exclusion criteria were as follows: (I) patients with disorders of sex development or abnormal chromosomes, (II) incomplete patient data, and (III) testicular nubbin or remnants removed at the time of surgical exploration.

For the independent validation cohort, we prospectively studied patients who underwent orchiopexy from January 2018 to December 2018 at Shenzhen Children's Hospital.

We used the following definitions: TV = length × width × height × 0.52. For unilateral UDT, testicular atrophy index (TAI) = (contralateral TV – affected TV)/contralateral TV × 100% (11). For patients with bilateral testicular diseases, TAI = (normal volume of testis – affected TV)/normal value of testis. TA was defined as a reduction of >50% of the TV compared to the contralateral, normally descended testis (TAI >50%) (12). The preoperative TV ratio was defined as the ratio of the affected TV to the contralateral TV. UDT was classified as follows: low-position UDT: testis found at the lower inguinal canal or external ring; middle position UDT: testis found in the middle or high inguinal canal; at the internal ring: peeping testis; and high position UDT: intra-abdominal testis.

The variables included age, laterality, testicular location, preoperative TV ratio, deferens and epididymis anomaly, hormonal treatment, comorbidities, type of surgical procedure, operating time, and complications. Age was classified into 5 groups: age <1 year; age ≥1 year but <2 years; age ≥2 years but <4 years; age ≥4 year but <6 years; and age ≥6 years. TV was tested by ultrasound, which was performed both prior to surgery and 1 year after surgery. Deferens and epididymis anomaly included looping vas deferens, absence of vas deferens, and disjunction between

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testis and epididymis.

Surgical procedures

Of the three main procedures, the choice of surgical procedure was surgeon-dependent and based on the testicular location. Usually, for low UDT, we performed open inguinal orchiopexy; for middle UDT, we performed open inguinal or laparoscopic orchiopexy. For an intra-abdominal testis, we performed laparoscopic orchiopexy, or two-stage Fowler-Stephens orchiopexy (FSO) if the testis was too high to undergo regular orchiopexy. During the surgery, the testis was located into the dartos pouch, and the stitch connected the lower pole of the testis to the inferior wall of the scrotum, to prevent testicular ascent.

Statistical analysis

All statistical analyses were performed using SPSS statistical software, version 17.0 (SPSS Inc., Chicago, Il, USA) and R software, version 3.2.5 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses included three phases: (I) univariate analysis of potential risk factors, (II) multiple logistic regression analysis for independent risk factors, and (III) validation of prediction models.

Univariate analysis was performed on all variables to determine their relationship with TA. The variables with P<0.1 were included in subsequent multiple variable analysis. Multiple logistic regression analysis was performed to analyze the independent risk factors predicting TA, and a nomogram was constructed to predict the probability of TA. Finally, after the stage of cross-validation, a receiver operating characteristic (ROC) curve was constructed to check the area under the curve (AUC), sensitivity, and specificity of the model.

Results

A total of 1,956 patients with UDT underwent orchiopexy from 2013 to 2017. Of these patients, 310 were excluded due to incomplete ultrasound results, while 38 were excluded due to the presence of disorders of sexual development or a testicular nubbin. A total of 1,608 patients were included in this study. The median age of the patients was 2.8 years (range, 0.5–11.3 years). We recorded low UDT in 373 cases, middle UDT in 1,041 cases, and high UDT in 194 cases. The mean TV was 0.27 mL. The demographic data and outcomes are summarized in *Tables 1,2*.

Open orchiopexy was performed in 1,002 cases, laparoscopic orchiopexy in 555 cases, and staged FSO in 51 cases. The median age of patients who underwent stage II FSO was 3.52 years, and the time intervals between stage I and stage II were 6–8 months. One hundred and thirty-three patients were associated with deferens and epididymis anomalies, including looping vas deferens, absence of vas deferens, and disjunction between testis and epididymis. There were 100 patients with comorbidities—64 with developmental delay and 36 with congenital heart disease.

The median duration of follow-up was 14 months (range, 12–18 months). A total of 228 (14.2%) patients developed TA. The atrophy rates of open orchiopexy, laparoscopic orchiopexy, and two-stage FSO were 10.8%, 16.4%, and 56.9%, respectively. The postoperative TA rates of low-, middle-, and high-position UDT were 5.6%, 12.3%, and 40.7%, respectively. The median age of TA patients was 2.6 years while undergoing surgery.

The results of the univariate analysis are summarized in *Table 3*. The potential predictors of TA were preoperative TV ratio (P=0.001), testicular location (P=0.001), surgical procedure (P=0.001), deferens and epididymis anomaly (P=0.001), and operating time (P=0.009). No significant differences were observed with respect to other variables such as age and comorbidities.

In a multiple variable analysis (*Table 4*), the independent predictors of TA were found to be preoperative TV ratio [odds ratio (OR) 0.001, 95% confidence interval (CI): 0.001–0.003, P=0.001], testicular location (OR 1.903, 95% CI: 1.368–2.649, P=0.001), deferens and epididymis anomaly (OR 6.470, 95% CI: 4.057–10.320, P=0.001), and two-stage FSO (OR 2.613, 95% CI: 1.022–6.677, P=0.04). The model suggested that the risk of TA was higher for patients with deferens and epididymis anomalies, higher testicular location, lower TV ratio, and in two-stage FSO. No other variables had P<0.05. We constructed a nomogram using these risk factors to predict the probability of TA (*Figure 1*). The performance of the nomogram was evaluated using a calibration plot (*Figure 2*).

Independent validation studies

From January 2018 to December 2018, 550 patients who underwent orchiopexy were included in the validation cohort (*Table 5*). Successful validation was achieved, and a ROC curve was constructed (*Figure 3*). In the ROC curve, the AUC was 0.851 (95% CI: 0.826–0.875) for the prediction model. When we chose a cutoff value of –1.79,

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Table 1 Characteristics of the 1,608 patients and the testicular atrophy data in training cohort

Variables	No.	Median age (years)	Atrophic testis	Percentage
Total	1,608	2.84	228	14.2%
Laterality				
Unilateral	1,422	2.63	200	14.1%
Bilateral	186	4.48	28	15.1%
Testicular location				
Low	373	2.92	21	5.6%
Middle	1,041	2.80	128	12.3%
High	194	2.93	79	40.7%
Testicular volume ratio				
<0.6	794	2.80	206	25.9%
≥0.6	814	2.89	22	2.7%
Comorbidities				
Patients with comorbidities	100	2.62	18	18.0%
Patients without comorbidities	1,508	2.86	210	13.9%
Deferens and epididymis anomaly				
Yes	133	2.15	70	52.6%
No	1,475	2.90	158	10.7%
Orchiopexy				
Open orchiopexy	1,002	3.11	108	10.8%
Laparoscopic orchiopexy	555	2.31	91	16.4%
Two-stage FSO	51	3.52	29	56.9%
Complication				
Yes	64	2.87	11	17.2%
No	1,544	2.84	217	14.1%
Age, years				
<1	184	0.8	14	7.6%
≥1, <2	744	1.4	128	17.2%
≥2, <4	303	2.7	49	16.2%
≥4, <6	192	4.8	23	12.0%
≥6	185	8.8	14	7.6%
UDT				
Primary	1,587	2.82	224	14.1%
Secondary	21	4.33	4	19.0%

FSO, Fowler-Stephens orchiopexy.

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Table 2 The clinical characteristics of patients with and without testicular atrophy

Variables	Patients with testicular atrophy	Patients without testicular atrophy	Total
No.	228	1,380	1,608
Age (years)	2.60	2.88	2.84
Testicular volume ratio	0.42	0.66	0.63
Operating time (min)	52.5	57.5	56.3
Laterality			
Unilateral	200	1,222	1,422
Bilateral	28	158	186
Testicular location			
Low	21	352	373
Middle	128	913	1,041
High	79	115	194
Comorbidities			
Patients with comorbidities	18	82	100
Patients without comorbidities	210	1,298	1,508
Deferens and epididymis			
Yes	70	63	133
No	158	1,317	1,475
Orchiopexy			
Open orchiopexy	108	894	1,002
Laparoscopic orchiopexy	91	464	555
Two stage FSO	29	22	51
Complication			
Yes	11	53	64
No	217	1,327	1,544

FSO, Fowler-Stephens orchiopexy.

the sensitivity was 78.1%, and specificity was 77.5%.

Discussion

To our knowledge, this is the largest series of pediatric orchiopexies reported from a single institution, and the first to be accompanied by a prediction model for assessing risk factors for TA. Our study illustrates that the incidence of TA is higher in patients with a lower TV ratio, higher testicular location, deferens and epididymis anomaly, and in two-stage FSO. As these factors could achieve an AUC of 0.85, it can be used as a prediction model. It has the potential to assist surgeons in choosing the optimal surgical procedure in UDT, and in predicting the probability of TA after orchiopexy, in addition to helping answer parents' questions about TA.

TA is the most severe complication of orchiopexy. In the literature, the incidence of TA after orchiopexy for UDT ranges from 8% to 32% with various criteria applied (6-9). TA is associated with azoospermia and infertility in adulthood. Sakamoto *et al.* found that smaller TV caused oligospermia and increased the risk of infertility (13). Similarly, Bellurkar at al. reported that testicular size correlated significantly with azoospermia and oligospermia, and could be used as a Parameter for Predicting Infertility (14). According to EAU guidelines on pediatric urology (2020), boys with one UDT have a lower fertility rate and the same paternity rate as those with bilateral normal testes. Boys with bilateral undescended testes suffer both lower fertility and paternity rates (15). TA in UDTs after orchiopexy tends to be secondary in most cases. TA may result from the following causes: tension in the spermatic cord with subsequent testicular ischemia, torsion of or injury to the spermatic cord when passing the testes to the scrotum, or insufficient collateral vessels after ligation of the spermatic cord in FSO.

There are a limited number of studies on the risk factors for TA, and only a few variables have been analyzed. Alagaratnam *et al.* reported an atrophy rate of 8.8% in a study on two-staged orchiopexy in 94 patients with intra-peritoneal testis (16). Ein *et al.* retrospectively studied 1,400 children undergoing orchiopexy and concluded that the most significant risk factors associated with TA were high testicle, vas problems, and preoperative torsion (9). However, the study did not include the type of surgical procedure and TV as variables. Moreover, prospective validation of the prediction model was absent. Thus, we conducted the present study with a large volume of samples, sufficient variables, and prospective validation of the model, in order to render it more scientifically robust. We were able to achieve an AUC of 0.851, a sensitivity of 78.1% and specificity of 77.5% with the validation model, thereby establishing our findings as a useful tool for predicting the probability of TA after orchiopexy and guiding doctors towards a suitable procedure for the management of UDT.

In the present study, the high testicular location was an independent risk factor for TA, presumably because the higher surrounding temperature in the inguinal

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Table 3 Univariate logistic regression analysis predicting testicular atrophy after orchiopexy

Predictor variable	P	OR (95% CI)
Testicular location	0.001	3.828 (2.933–4.998)
Preoperative volume ratio	0.001	0.001 (0.001–0.010)
Deferens and epididymis anomaly	0.001	9.262 (6.345–13.2)
Age	0.112	0.952 (0.896–1.011)
Surgical procedure	0.001	2.323 (1.835–2.939)
Complication	0.689	1.183 (0.520–2.69)
laterality	0.492	0.928 (0.749–1.149)
Hormonal treatment	0.586	1.185 (0.643–2.184)
Comorbidities	0.609	1.146 (0.679–1.936)
Operating time	0.009	0.991 (0.985–0.998)

OR, odds ratio; CI, confidence interval.

Table 4 Multiple variable logistic regression analysis predicting testicular atrophy after orchiopexy

Risk factor	OR	95% CI	P	B regression coefficient
Testicular location	1.903	1.368–2.649	0.001	0.644
Preoperative volume ratio	0.001	0.001–0.003	0.001	–7.027
Deferens and epididymis anomaly	6.470	4.057–10.320	0.001	1.867
Open orchiopexy	Referent			
Laparoscopic orchiopexy	0.541	0.286–1.022	0.060	–0.614
Two stage FSO	2.613	1.022–6.677	0.040	0.960
Operating time	0.992	0.983–1.001	0.082	–0.008

FSO, Fowler-Stephens orchiopexy; OR, odds ratio; CI, confidence interval.

canal and abdomen damages the cells of the testis. The maldescended testis suffers heat stress when not at the lower scrotal temperature (33 ℃), which in-turn interferes with testicular physiology and the development of germ cells into spermatogonia (17). Chi-shin Tseng showed that the incidence of TA was higher when patients had high primary testicular location (18). A previous study reported that the preoperative location of UDT did not affect the final changes in TV in patients who received preoperative hormone therapy, however, this study had a small sample size (only 75 patients) (19). Our research, on a greater sample size (1,608 patients), contradicted this result, concluding that the primary location of UDTs did have an impact on TA.

The preoperative TV ratio is the most important factor affecting TA. The smaller the testes, the higher the atrophy rate. The smaller size of the testis reveals the damage of germ cells and Leydig cells (20), thereby predisposing to TA after surgery. In our study, the TA rate increased significantly when the preoperative TV ratio was below 0.6. Although Chi-Shin Tseng reported that the post-orchiopexy volumes of UDTs actually increased in size on follow-up, they were notably still smaller than the normal values (21). Jedrzejewski *et al.* reported the TV ratio increased after orchiopexy, which indicated that most undescended testes would have catch-up growth after a long follow-up period. However, testes with an initial ratio <0.25 did not show any significant growth (22).

Deferens and epididymis anomaly is another risk factor for TA. Deferens and epididymis anomalies mainly include looping vas deferens, absence of vas deferens, and disjunction between testis and epididymis. The disjunctions

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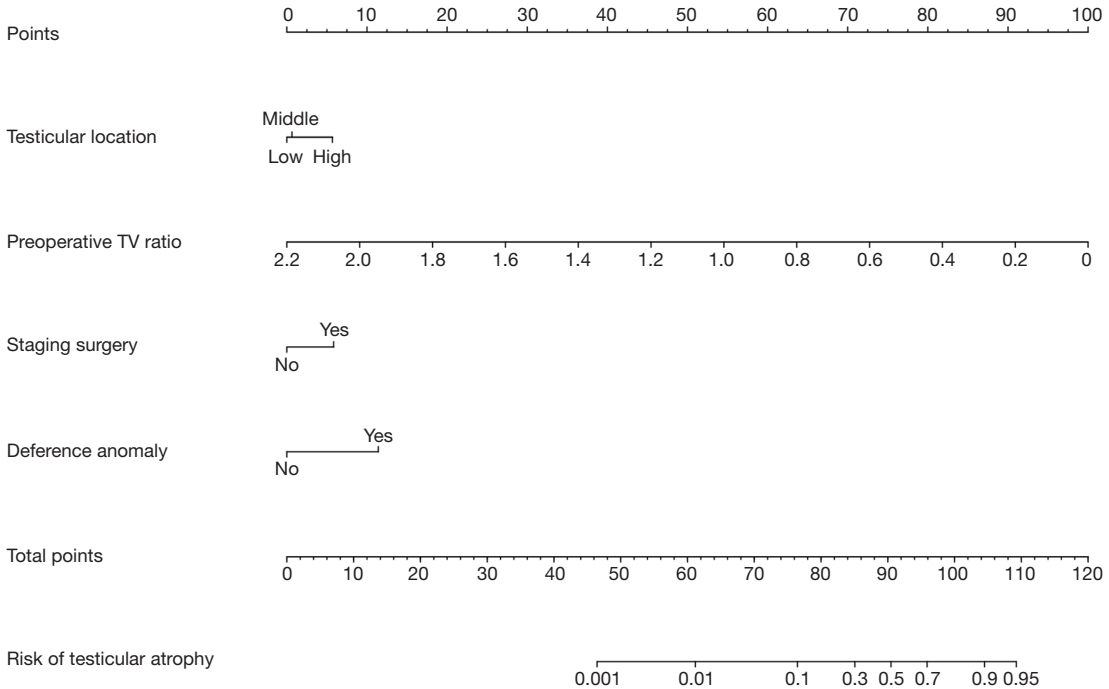

Figure 1 Nomogram for the prediction of testicular atrophy after orchiopexy in children. Staging surgery, two-stage Fowler-Stephens orchiopexy. TV, testicular volume.

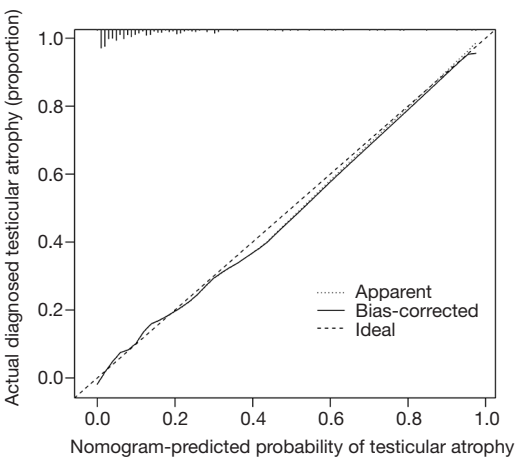

Figure 2 Calibration plot for the nomograms for the probability of testicular atrophy after orchiopexy.

between testis and epididymis consist of epididymal head non-fusion, epididymal tail non-fusion, and complete non-fusion (23). As deferens and epididymis anomaly is an important index of gonadal hypoplasia, it can affect the development of the testis and cause TA. Moreover, in cases with a looping vas, laparoscopic dissection of the spermatic cord can potentially cause injury to the deferential artery itself, leading to testicular ischemia (24). Similarly, Ein *et al.* reported that vas problems could cause TA (9).

The decision on which surgical procedure to perform is surgeon-dependent. Anatomical factors, comfort with laparoscopic procedures, and long-standing clinical practice patterns undoubtedly affect this decision. This study found that the atrophy rate was higher in two-stage FSO than in regular orchiopexy. Similarly, a systematic review demonstrated that two-stage FSO had a higher atrophy rate than routine orchiopexy (25). Stec *et al.* reported that the type of surgical procedure was predictive of the success of intra-abdominal testicular surgery (8). As two-stage FSO is associated with a higher risk of TA, it might be advisable to avoid the use of this procedure, and regular orchiopexy without vessel division can be attempted first whenever possible. For the intra-abdominal testis not amenable to regular laparoscopic orchiopexy, a novel technique of two-stage laparoscopic traction-orchiopexy may be an alternative, which has a high success rate and low atrophy rate according to reports (26). This procedure preserves spermatic vessels, so it could reduce TA.

Age is reportedly an important factor to consider while planning surgery for UDT (20). Any kind of treatment leading

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Table 5 Characteristics of the 534 patients and the testicular atrophy data in validation cohort

Variables	No.	Mean age (years)	Atrophic testis	Percentage
Total	534	2.83	87	16.3%
Laterality				
Unilateral	474	2.70	82	17.3%
Bilateral	60	3.83	5	8.3%
Testicular location				
Low	120	2.94	9	7.5%
Middle	349	2.69	59	16.9%
High	65	3.29	19	29.2%
Testicular volume ratio				
<0.6	258	2.85	72	27.9%
≥0.6	276	2.81	15	5.4%
Comorbidities				
Patients with comorbidities	57	3.46	9	15.8%
Patients without comorbidities	477	2.75	78	16.4%
Deferens and epididymis				
Yes	51	2.12	22	43.1%
No	483	2.90	65	13.5%
Orchiopexy				
Open orchiopexy	319	3.09	40	12.5%
Laparoscopic orchiopexy	189	2.24	38	20.1%
Two stage FSO	26	3.87	9	34.6%
Complication				
Yes	9	2.91	1	11.1%
No	525	2.82	86	16.4%

FSO, Fowler-Stephens orchiopexy.

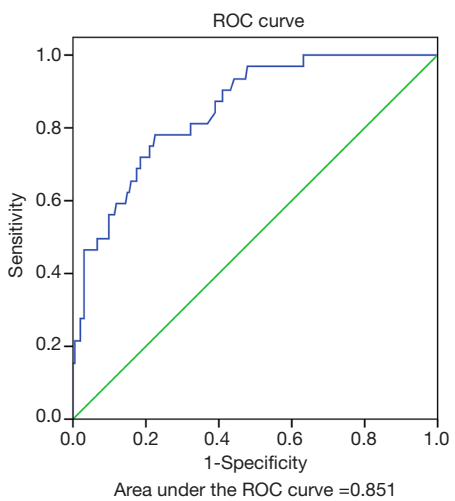

Figure 3 Receiver operating characteristic curve (ROC) of the multivariable logistic regression model for the prediction of testicular atrophy after orchiopexy. The area under the curve (AUC) was 0.851.

to a scrotal positioned testis should be completed by 12 months of age, or by 18 months at the latest, because histological examinations of UDT have revealed a progressive loss of germ cells and Leydig cells past that age (20). Supporting the idea of an earlier operative approach, Michikawa *et al.* showed that orchiopexy at less than 2 years of age prevented morphological changes in the testis of patients with UDT (27). Many studies have revealed better testicular growth after early orchiopexy (28,29). Carson *et al.* reported that the TA rate was lower for orchiopexy performed before the age of 13 months than for those aged 13–24 months (5% *vs.* 12%) (30). In contrast, Chi-shin Tseng reported that early orchiopexy before 2 years of age, might be associated with higher TA risk (18). However, in the present study, we did not find any correlation between TA and age at surgery. The testicular damage caused by older age was perhaps not obvious in cases with greater TV.

Boehme *et al.* reported that acquired UDT usually

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accounts for a significant proportion of "late" orchiopexies in patients with UDTs (31). In our study, most patients had primary UDT, and only 21 patients had secondary UDT. The age for surgery in secondary UDT was older than that for primary UDT, but the atrophy rate was not statistically different between the two groups.

The definition of TA remains controversial. Recently, it has been classified into complete and relative atrophy (32). Complete atrophy is defined as a nubbin in the scrotum without vascular flow, which is very rare after orchiopexy (32). In the present study, TA referred to relative atrophy and was defined as a reduction of >50% of the TV compared to the contralateral normal testis (TAI >50%) in unilateral UDT—a definition used by most clinicians (12). As TAI is an objective tool for qualifying patients with UDT for surgery as well as for monitoring surgical outcomes (33), it is universally used to assess TA. For bilateral UDT, the TV of the affected testis is compared with the normal TV. However, various criteria for TA have been adopted in different studies. Ein *et al.* defined TA as TAI >33% (9). One study defined TA as >50% loss of TV or a postoperative TV <25% of the contralateral TV. In the aforementioned study, however, the TV was assessed by clinical palpation (10), while others have employed an orchidometer (12,32). Such methods are not as accurate as ultrasound, and the atrophy rate is usually underestimated. In the present study, the TV was checked by ultrasound, which provided an objective index for testicular development.

Previous studies have not identified the preoperative TV ratio as a risk factor for TA. Our findings differ from previous studies on the effect of TV ratio, probably because many other variables were included in our research, and all patients had sufficient ultrasound data. Thus, preoperative ultrasound testing is necessary to assess the TV and to determine the risk of TA.

Our study has several strengths, such as the large sample size, inclusion of sufficient clinical variables, accurate measurement of TVs through ultrasonography, and prospective validation of the prediction model.

We acknowledge there are some limitations in the present study as well. First, it was a single-center study. Second, the procedures were performed by different surgeons, which may induce a selection bias. Finally, long-term follow-up is needed to confirm these initial findings.

Conclusions

The present study provides the risk factors for predicting TA after orchiopexy in UDT. In patients with UDT, excluding those with chromosomal abnormalities and testicular nubbin, the incidence of TA is higher in patients with a low TV ratio, high testicular location, deferens and epididymis anomaly, and in two-stage FSO. This prediction model provides good evidence for surgeons to choose the appropriate surgical procedure in UDT and predict the probability of TA. However, long-term follow-up is needed to confirm these initial findings.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Institutional Review Board of Shenzhen Children's Hospital (2019007). It is an observation study, and the data are anonymous, so the informed consent was waived.

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