Predictive factors for successful sperm retrieval by microdissection testicular sperm extraction in men with nonobstructive azoospermia and a history of cryptorchidism

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This study aims to explore the factors influencing the success rate of the microdissection testicular sperm extraction (Micro-TESE) in patients with nonobstructive azoospermia (NOA) and cryptorchidism. Clinical data of 162 patients with cryptorchidism who underwent Micro-TESE due to infertility from December 2015 to May 2020 in the First Affiliated Hospital of Nanjing Medical University were analyzed retrospectively. In the univariate analysis, significant differences in the age of patient at the time of orchidopexy (median [interquartile range, IQR]: 7.0 [4.0–11.0] years vs 11.5 [9.0–14.5] years, \( P < 0.001 \)), interval between orchidopexy and Micro-TESE (mean ± standard deviation: 17.5 ± 5.0 years vs 14.4 ± 4.4 years, \( P < 0.001 \)), severity of cryptorchidism (unilateral [62.8%] vs bilateral [31.6%], \( P < 0.001 \)), location of cryptorchidism, intra-abdominal [27.3%] vs inguinal [44.8%] vs suprascrotal [66.7%], \( P < 0.001 \)), volume of the dominant testis (median [IQR]: 17.00 [15.00–19.00] ml vs 14.50 [11.75–16.25] ml, \( P < 0.001 \)), and levels of follicle-stimulating hormone (FSH; \( P = 0.004 \)) and testosterone (\( P = 0.006 \)) were observed between the successful and failed sperm extraction groups. After conducting the multivariate analysis, four of these factors, including unilateral/bilateral cryptorchidism (\( P < 0.001 \)), location of cryptorchidism (\( P = 0.032 \)), age of orchidopexy (\( P < 0.001 \)), and dominant testicular volume, were adopted in the clinical prediction model to evaluate preoperatively the success rate of Micro-TESE for patients with NOA and cryptorchidism. The likelihood of successful sperm retrieval by Micro-TESE in men with NOA and cryptorchidism increased in patients with mild forms of cryptorchidism.

Keywords: azoospermia; cryptorchidism; microdissection testicular sperm extraction; predictive
and less than a week. Semen analysis was performed in accordance with the Fifth Edition of Semen Analysis Standards formulated by the World Health Organization (WHO).\textsuperscript{12} The parameters evaluated were seminal volume, sperm concentration, sperm viability, sperm motility, and sperm morphology. If no sperm was found in two or more specimens from patients by microscopy after semen centrifugation, these patients were diagnosed with azoospermia. Then, significant outcomes of clinical examinations, which included small testis volume (<10 ml), high or low serum follicle-stimulating hormone (FSH) level (two times higher or more), and no obstructive sign of reproductive system from ultrasound, could help establish the diagnosis of NOA. For ambiguous cases, surgical investigations, like testicular sperm aspiration (TESA), were conducted to ensure that those included in further study was nonobstructive.

NOA with cryptorchidism was diagnosed when meeting all following criteria: (1) a clear history of cryptorchidism after birth, small or normal testis volume, and high or normal FSH level; (2) a clear outcome of no obstructive sign of reproductive system from ultrasound or no sperm extraction from TESA; (3) reliable histopathology data and results proving impaired functions of producing sperm in testis; and (4) exclusion of other possible causes of NOA (e.g., chromosome examination shows no microdeletion of Y chromosome). The inclusion criteria were as follows: (1) preoperatively diagnosed as NOA with cryptorchidism and (2) a history of orchidopexy.

As a result, 192 patients were excluded, and 162 patients (aged 21–30 years with a median age of 26 years) were enrolled. Among the 162 patients, 86 had unilateral cryptorchidism, and 76 had bilateral cryptorchidism; and 44 had abdominal cryptorchidism, 58 had inguinal cryptorchidism, and 60 had suprascrotal cryptorchidism. Besides, among 54 patients with a history of varicocele, 31 underwent varicocelectomy, and 23 did not.

**Operation method**

The larger testis was chosen as the dominant side for operation. The tunica vaginalis was opened and cut 1.5–2.5 cm laterally on the ventral side of the testis. For bipolar electrocoagulation hemostasis, the testis was gently squeezed, and the tunica albuginea of the testis was cut along the coronal plane to expose the operative field of vision fully. If needed, seminiferous tubules were exposed and rinsed with normal saline to keep the field of vision clear. An operating microscope (ECLIPASE TS100, Nikon, Shanghai, China) at $20\times$–$25\times$ magnification was used to examine the testicular parenchyma directly. First, superficial dilated tubules with a high possibility of sperm were isolated under the microscope and placed in a sterile culture dish with sperm transport buffer. The structure of tubules was destroyed and observed under high-power microscopy. If no sperm was observed, the suspension would be conscientiously checked after centrifugation. If enough sperm was available for ICSI and cryopreservation, the operation was stopped. If motile sperm was not enough, the incision was further enlarged to explore the upper and lower poles of the testis. The testicular parenchyma was fixed on the sides of the incision and the ipsilateral tunica albuginea to avoid damaging the connection between the tunica albuginea and the testicular parenchyma, which could probably cause hemorrhage or hematoma. The upper pole of the testis was dissected, and blood vessels were carefully identified to avoid damage. Multiple longitudinal incisions were made between the testicular septum to achieve the deepest level of anatomy. Full and opaque tubules were selected, and the above steps of sperm microscopy were repeated. If motile sperm was not enough, the inferior pole of the testis was explored in the same way above. If no sperm was found, the operation was stopped, and the tunica albuginea of the testis was sutured. The testis was also included in the tunica vaginalis, and the incision was sutured. At any step, if enough motile spermatozoa were found, the operation was finished.

**Statistical analyses**

Data were processed using the SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA) and R software 3.6.2 (Bell Laboratories, Murray Hill, NJ, USA) for Windows. Mean ± standard deviation (s.d.) was used for normal distribution data, and the median (IQR) was used for nonnormal distribution data. The Student's t-test was used to compare the mean of two independent samples that followed a normal distribution, whereas the nonparametric test was used to compare two independent samples that did not follow a normal distribution. The percentage was used to express the count data. The Pearson $\chi^2$ test was used to compare groups. Statistical significance was considered at $P < 0.05$. Variables that were statistically significant ($P < 0.05$) in the univariate analyses were included in the multivariate analysis by using the binary logistic regression model. A prediction model for the success rate was generated on the basis of the logistic regression analysis, and the nomogram of the clinical prediction model was drawn using the R software. The goodness assessment of the regression model and nomogram was conducted to measure discrimination and calibration. The receiver operating characteristic (ROC) and discrimination curves were plotted using the R software, and their area under the curve (AUC) and C-statistic were calculated. An internal invalidation was conducted using 1000-bootstrap resamples by using the SPSS 23.0 to avoid optimism.

**RESULTS**

In our study, 162 patients all experienced a Micro-TESE in our hospital due to a history of infertility caused by NOA. These patients' age ranged from 24 years to 31 years and all had a history of cryptorchidism. Testicular sperm was successfully retrieved in 78 (sperm retrieval rate [SRR] of 48.1%) of 162 cases. The sperm samples extracted from patients were cryopreserved in the sperm bank of our hospital. Until the date of writing, 54 patients had undergone ICSI, of which 36 (66.7%) cases had successful delivery, 14 (25.9%) cases had termination of pregnancy due to factors (such as fetal arrest), and 4 (7.4%) patients’ spouses were still pregnant.

As shown in Table 1, among 54 patients with varicocele, 20 (64.5%) succeeded in sperm extraction among 31 patients with a history of varicocelectomy, while 9 (39.1%) succeeded in 23 patients who did not receive surgical repair. The result showed that varicocelectomy does not significantly affect the success rate of Micro-TESE. By comparing the success rate between 86 patients with unilateral cryptorchidism and 76 patients with bilateral cryptorchidism, it could be determined that unilateral cryptorchidism brings better sperm retrieval outcome ($P < 0.001$). When comparing different locations of cryptorchidism including intra-abdominal, inguinal, and suprascrotal cryptorchidisms, we found that the type of suprascrotal achieved the highest SRR with a rate of 66.7%, and the differences made significance ($P < 0.001$). Besides, there are significant differences in the median age ($P < 0.001$) and mean interval ($P < 0.001$) between successful and failed group. The analysis on volume of dominant testis indicated that bigger testis volume led to a better outcome of Micro-TESE ($P < 0.001$). Among 162 patients, 24 of them submitted their genetic test result and 13 patients turned out to be congenital.

Patients were divided into two groups in accordance with their history of varicocelectomy, i.e., positive and negative. The age of orchidopexy, dominant testicular volume, and levels of FSH and
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Table 1: Clinical characteristics of the study patients and single factor analysis

| Characteristic | Total | Success | Failure | P    |
|----------------|-------|---------|---------|------|
| Age (year), median (IQR) | 27.0 (24.0–31.0) | 28.0 (26.0–31.0) | 26.0 (24.0–28.0) | 0.345 |
| BMI (kg m⁻²), median (IQR) | 24.1 (22.3–26.1) | 23.8 (22.1–26.0) | 24.4 (22.6–26.9) | 0.138 |
| Varicocelectomy, n (%) | 0.064 |
| Positive | 31 (57.4) | 20 (64.5) | 11 (35.5) | <0.001 |
| Negative | 23 (42.6) | 9 (39.2) | 14 (61.8) | <0.001 |
| Cryptorchidism, n (%) | <0.001 |
| Unilateral | 86 (53.1) | 54 (62.8) | 32 (37.2) | <0.001 |
| Bilateral | 76 (46.9) | 24 (31.6) | 52 (68.4) | 0.004 |
| Location, n (%) | <0.001 |
| Intra-abdominal | 44 (27.2) | 12 (27.3) | 32 (72.7) | <0.001 |
| Inginal | 58 (35.8) | 26 (44.8) | 32 (55.2) | 0.004 |
| Suprascrotal | 60 (37.0) | 40 (66.7) | 20 (33.3) | 0.004 |
| Age of orchidopexy (year), median (IQR) | 10.0 (6.0–13.0) | 7.0 (4.0–11.0) | 11.5 (9.0–14.5) | <0.001 |
| Interval time (year), median±s.d. | 15.88±4.95 | 17.49±5.03 | 14.38±4.39 | <0.001 |
| Dominant testicular volume (ml), median (IQR) | 15.0 (13.0–17.0) | 17.0 (15.0–19.0) | 14.5 (12.0–16.0) | <0.001 |
| Testosterone (nmol l⁻¹), mean±s.d. | 16.81±5.58 | 15.58±5.83 | 17.96±5.10 | 0.006 |
| FSH (IU l⁻¹), median (IQR) | 17.0 (11.7–23.3) | 19.8 (13.2–25.7) | 14.9 (10.8–20.5) | 0.004 |
| LH (IU l⁻¹), median (IQR) | 6.16 (4.70–8.00) | 5.67 (4.46–8.06) | 6.49 (5.02–7.95) | 0.075 |

s.d.: standard deviation; IQR: interquartile range; FSH: follicle-stimulating hormone; LH: luteinizing hormone; BMI: body mass index

luteinizing hormone (LH) were divided into high and low groups in accordance with the median. Then Pearson χ² test was used to explore correlations between these factors and the results of Micro-TESE. Correspondingly, the Students’ t-test was utilized to analyze whether the interval and the testosterone level could affect the results of Micro-TESE. As a result, no significant correlation was found between the results of Micro-TESE and the history of varicocelectomy (P = 0.064). Factors that showed significant differences between groups included the severity of cryptorchidism (unilateral/bilateral, P < 0.001; location of cryptorchidism, P < 0.001), age of orchidopexy (P < 0.001), interval time (P < 0.001), volume of dominant testis (P < 0.001), and levels of testosterone (P = 0.006) and FSH (P = 0.004). Besides, no significant relationship was observed between the Micro-TESE result and LH level (P = 0.075) and between patients’ age and body mass index (BMI), as shown in Table 1.

Given the evident analogy between the age of patient at the time of orchidopexy and the interval between orchidopexy and Micro-TESE, the inclusion of these variables into the regression analysis model was unreasonable. Eventually, we suggested that the age of patient at the time of orchidopexy improved due to its intuitive way of determining whether patients avoided early testicular damage. Overall, the severity of cryptorchidism (unilateral/bilateral and location of cryptorchidism), age of patient at the time of orchidopexy, dominant testicular volume, and FSH level were included in the logistic regression model for multivariate analysis. Ultimately, we obtained a satisfying model through the logistic regression analysis of predicting factors associated with the result of Micro-TESE, including the severity of cryptorchidism (unilateral/bilateral, P < 0.001; and location of cryptorchidism, P = 0.032), age of orchidopexy (P < 0.001), and dominant testicular volume (P < 0.001), as shown in Table 2.

Based on the logistic regression analysis, the clinical prediction model was obtained using the R software and the nomogram was drawn (Figure 1). By mapping the value of each factor to the “points” axis, the points of probability of successful Micro-TESE for each variable were obtained, and the total points can be calculated by summing them up. In the end, the success rate was easy to recognize on the probability axis at the bottom in accordance with the total points. It can be concluded from the nomogram that a higher score of the patient is accompanied by a higher success rate of Micro-TESE. Specifically, each patient’s clinical parameters were assigned with specific points. The specific operative method is as follows: sum the points of each clinical parameter to get the final score and map it to the “Probability” axis to determine the success or failure of the extraction. For the position of cryptorchidism, intra-abdominal was assigned 30 points, inguinal was assigned 20 points, and suprascrotal was assigned 10 points. For unilateral and bilateral cryptorchidism, 40 points were assigned to unilateral cryptorchidism, and failure of the extraction. For the position of cryptorchidism, suprascrotal was assigned 10 points. For unilateral and bilateral cryptorchidism, 40 points were assigned to unilateral cryptorchidism, and no point is assigned to the latter. For the patients of different
orchidopexy ages, their points were uniformly distributed between 0–88 points (0 year old was assigned 88 points and 24 years old was assigned 0 point). Similarly, the points for the dominant testicular volume are evenly distributed between 0–100 (8 ml is assigned 0 point and 24 ml is assigned 100 points). For example, as the nomogram indicates, for a 24-year-old patient with a testicular volume of 20 ml and a cryptorchidism position of suprascrotal, the total points for him is about 30 + 0 + 0 + 75 = 105 points, and the mapping success rate is about 0.15. In addition to predicting the effectiveness of Micro-TESE on patients with diverse clinical characteristics, the prediction model demonstrated that the severity of cryptorchidism had the highest effect on total score, which could consequently be concluded as the key factor affecting the success rate of Micro-TESE. Discrimination measurement through ROC curve (Figure 2) and calibration measurement through calibration curve (Figure 3) were conducted to evaluate the prediction model. Results showed that the AUC for the model was 0.907 (95% confidence interval [CI]: 0.887–0.926), and the C-statistic for the model was 0.907 (95% CI: 0.879–0.928). To avoid optimism, we conducted internal invalidation by using 1000-bootstrap resamples. The C-index after bootstrapping was 0.892 (95% CI: 0.873–0.911).

DISCUSSION

From December 2015 to May 2020, our center conducted Micro-TESE on 162 patients with NOA and history of cryptorchidism. By analyzing their clinical characteristics and correlated outcomes, we found that the low severity of cryptorchidism (unilateral and lower cryptorchidism), early time of receiving orchidopexy, large dominant testis, and long recovery time after orchidopexy were tightly related to a successful Micro-TESE. The preoperative levels of testosterone, LH, and FSH failed to show significant associations with the success rate of Micro-TESE in the present study.

The incidence of cryptorchidism was reported to be approximately 2%–5% in newborns and 21% in premature infants, and is inversely proportional to the gestational age and birth weight. In the normal pregnancy process, the transient increase in testosterone levels in the third month after birth enables the testis to continue to decline. After nine months, the incidence of persistent cryptorchidism remains at approximately 1%. The pathogenesis of cryptorchidism remains unclear but is commonly considered to be related to genetic, endocrine, and environmental factors. Despite the absence of a well-recognized treatment, Orchidopexy is usually conducted to correct the abnormal anatomical position and avoid secondary damage on the testis caused by high temperature. According to the sperm analysis of 251 adult males who had undergone orchidopexy in infancy reported by Gracia et al., the sperm quality of patients with

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Table 2: Multivariate analysis of factors associated with success rate of microdissection-testicular sperm extraction

| Factor                      | OR    | 95% CI          | P   |
|-----------------------------|-------|-----------------|-----|
| Locationa                   | 0.479 | 0.245–0.936     | 0.032|
| Unilateral or bilateralb    | 0.017 | 0.003–0.088     | <0.001|
| Age of orchidopexy (year)  | 0.753 | 0.654–0.866     | <0.001|
| Dominant testicular volume (ml) | 2.178 | 1.567–3.027     | <0.001|

*aSuprascrotal cryptorchidism vs inguinal and intra-abdominal cryptorchidism. bBilateral vs unilateral. OR: odds ratio; CI: confidence interval

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Figure 2: ROC curve of the nomogram for success rate prediction model. The solid line represents the ability of the prediction model discriminating the actual successful sperm retrieval patients from the failed ones. More closer to the (0,1) means a better performance for the curve. AUC for ROC curve is 0.907 (95% CI: 0.887–0.926). ROC: receiving operating characteristic; AUC: area under curve; CI: confidence interval; Micro-TESE: microdissection testicular sperm extraction.

Figure 3: Calibration curve of the nomogram for success rate prediction model. The x-axis represents the predicted success rate of Micro-TESE. The y-axis represents the actual successful sperm retrieval (SSR) by Micro-TESE. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction. C-statistics for calibration curve is 0.907 (95% CI: 0.879–0.928). CI: confidence interval; Micro-TESE: microdissection testicular sperm extraction.
bilateral cryptorchidism is significantly lower than that of patients with unilateral cryptorchidism. Besides, Sangster et al.\textsuperscript{26} found that Micro-TESE following adult orchidopexy for inguinal testicles can result in a successful sperm retrieval (SSR) in over 1/3\textsuperscript{rd} of patients. Notably, even if the testis position is corrected, aberrant hormone levels are still inclined to compromise the development of spermatogonia to different degrees.\textsuperscript{27,28} This finding was consistent with results in our research, which revealed that the success rate of Micro-TESE in unilateral/low-positional cryptorchidism was higher than that in bilateral/high-positional cryptorchidism. The spermatogenesis function of most patients with severe cryptorchidism (bilateral cryptorchidism and high position of cryptorchidism) remained poor after orchidopexy. It is worth noting that 24 patients had made a genetic test to determine the cause of azoospermia. Five of them turned out to obtain azoospermia factor microdeletion, including 2 of azoospermia factor a (AZFa)/AZFb and 3 of AZFc, which probably indicated congenital azoospermia instead of cryptorchidism-derived infertility.\textsuperscript{29} Despite the low incidence of Y chromosome microdeletion in male infertility, it could instead of cryptorchidism-derived infertility. AZFb and 3 of AZFc, which probably indicated congenital azoospermia caused of azoospermia. Five of them turned out to obtain azoospermia factor microdeletion, including 2 of azoospermia factor a (AZFa)/AZFb and 3 of AZFc, which probably indicated congenital azoospermia instead of cryptorchidism-derived infertility.\textsuperscript{29} Despite the low incidence of Y chromosome microdeletion in male infertility, it could be a confounder of our study, and further research should avoid this.

A previous study showed that the degree of fertility decline depends on the continuously hiding time of testis.\textsuperscript{30} Virtanen et al.\textsuperscript{31} reported that 76% of patients with bilateral cryptorchidism who underwent orchidopexy at age of 10 months to 4 years have normal sperm count in adulthood, whereas only 26% of patients with bilateral cryptorchidism who underwent orchidopexy at the age of 4 years to 14 years have normal sperm count in adulthood. In patients with unilateral cryptorchidism, the effect of early orchidopexy is minimally significant, i.e., 75% in the 10-month-old to 6-year-old group vs 71% in the 9–12-year-old group.\textsuperscript{32} In the histological view, at three months, spermatocytes begin to transform into dark type A spermatagonia. During this period, the number of such spermatagonia in boys and infants with cryptorchidism is significantly reduced. The cryptorchidism testis changes under an electron microscope at the age of 1–2 years and histologically changes at the age of 2–3 years, and macroscopic atrophy occurs at the middle stage of childhood.\textsuperscript{33,34} Hence, the early performance of orchidopexy results in favorable testicular spermatogenic functions. In the present study, we observed that the success rate of Micro-TESE was remarkably correlated with the time the patients received the operation. For 78 patients with successfully retrieved NOA and cryptorchidism, the median age of undergoing orchidopexy was 7.0 (4.0–11.0) years. However, it was with a distinction of nearly 5 years old for the opposite group of 84 patients, whose was 11.5 (9.0–14.5) years old. Bojan and Ursula\textsuperscript{35} pointed out that orchidopexy before 8 years old in childhood would bring better prognosis for fertility compared with the later ones. It has now been a common sense in China that orchidopexy should be conducted no later than 2 years old to avoid permanent damage to reproductive function. Relatively, the median age of 7.0 (4.0–11.0) years is not of much satisfaction. The reason of delayed operation could be that treatment is limited by the low diagnostic and therapeutic level in Chinese basic hospitals. Considering they were mainly from less developed areas like countryside, they did not ask for medical help until growing into adults. Besides, the minimum age of receiving the orchidopexy was 1 year, which resulted in a surgical outcome with remarkable success. Our study clearly showed that early surgical repair for cryptorchidism in childhood resulted in improved prognosis of Micro-TESE for NOA in adulthood.

Koni et al.\textsuperscript{36} showed that in uncorrected adolescent cryptorchidism, more than 50% of patients have mature germ cells at different stages in their testes and that all patients have immature germ cells in their testes. Virtanen et al.\textsuperscript{31} reported that 28% of adult men with bilateral cryptorchidism have normal sperm count after the operation. These findings indicate that damage to testicular spermatogenesis caused by cryptorchidism is minimally pronounced in some patients, reversible to some extent, and primarily depends on the time of undergoing orchidopexy. Our results also showed that a long interval increased the likelihood of recovery and sperm reproduction of the spermatogenic system and high success rate of microsurgery. Nevertheless, in multivariate analysis, the interval between the two operations was not included in the model due to its unavoidable limitation of showing only “period” instead of exact “point” when compared with the age of orchidopexy along with its protective effects on spermatogenesis. An early time of orchidopexy is inevitably accompanied by a long interval.

Varicocele is a common correctable cause of male infertility in the field of reproductive medicine and has an incidence of 15% in healthy men and about 35% in patients with primary infertility.\textsuperscript{37} Varicoceles normally exert negative effects on semen quality, sperm function, and reproductive hormones, and varicocelectomy can effectively repair the damage on fertility and increase the chance of being fertilized.\textsuperscript{38} In the study of Sajadi et al.,\textsuperscript{39} the SRR in men with NOA and without clinical varicocele (22%) is lower than that in men who had undergone varicocelectomy (36%). Moreover, the live birth rate of men with NOA and varicocelectomy (23%) is higher than that of men with NOA and without varicocelectomy (11%). Haydardedeoglu and colleagues compared patients with NOA and a history of varicocele and patients with NOA alone, and found that the SRR of Micro-TESE in patients who underwent repair surgery for varicocele is significantly higher, suggesting that varicocelectomy for patients with NOA may have an improved effect on the results of Micro-TESE.\textsuperscript{37} In our study, 31 out of 54 patients with varicocele received surgical repair before the micro-TESE, and the SRRs for patients who had and had not undergone varicocelectomy were 65% and 39%, respectively. However, statistical analysis did not show significant differences (\(P = 0.06\)), which could probably be attributed to the small sample size of patients with varicocele in our study.

FSH is a glycoprotein produced by gonadotropin-releasing hormone, which stimulates the pituitary gland. FSH binds to the receptors of the supporting cells in the testes to promote the maturation of germ cells.\textsuperscript{38} Aydos et al.\textsuperscript{39} showed that among patients with NOA, the SRR of Micro-TESE on the experimental group receiving exogenous FSH treatment (64%) was almost twice that on the control group (33%). However, Sacca et al.\textsuperscript{40} reported no statistical differences between positive and negative SRR regarding mean FSH. Besides, a large-scale meta-analysis study enrolling 1248 patients showed no significant relationship between FSH levels and the final SRR.\textsuperscript{41} The conflicting results may suggest the complex role of sexual-related hormones, like FSH, in regulating spermatogenesis and male reproductive function. In the present study, high FSH levels exhibited a significant correlation with improved outcome of micro-TESE in patients with NOA in the univariate analysis but failed to show a significant correlation in the multivariate analysis. Thus, we did not include FSH levels in the final prediction model. The preoperative FSH level cannot become a reliable assistant biomarker for clinicians yet to determine the treatment strategy for patients with NOA.

Through retrospectively analyzing 162 cases of testicular microsurgery for infertility due to NOA, we concluded that a remarkable success rate of Micro-TESE was significantly associated with low severity of cryptorchidism (unilateral and low cryptorchidism), early time of orchidopexy, large dominant testis, and long recovery time after orchidopexy. On the basis of logistic regression analysis, we also generated the prediction model for clinical practice in judging the success rate of Micro-TESE for patients with NOA and a history of cryptorchidism, and the evaluation of discrimination and calibration revealed the good prediction capability of our model.
Nonetheless, given the small sample size and the relatively rough classification of cryptorchidism, results should be further elucidated. The right time to conduct Micro-TESE to improve the outcome of surgery, avoiding unnecessary trauma, and striving for improved long-term fertility may be worth studying in this field.

CONCLUSION
Our study revealed that four factors including unilateral/bilateral cryptorchidism, location of cryptorchidism, age of orchidopexy, and dominant testicular volume could together cooperatively evaluate the success rate of Micro-TESE for patients with NOA and cryptorchidism. Furthermore, the low severity of cryptorchidism results in minimal damage to the reproductive function. Orchidopexy should be conducted as soon as possible to achieve improved reproductive function in early infancy and childhood. If the treatment of cryptorchidism is delayed, sufficient recovery time is helpful for the restoration of spermatogenic function.

AUTHOR CONTRIBUTIONS
XLC and YAW initiated the conception and designed the study. SFS and CQ provided administrative support. ZWL, GYL, and DZ collected and assembled the patient’s data. XHY, YAW, and ZX analyzed and interpreted the data. XLC and XHR completed the figures. XLC wrote the manuscript. YAW reviewed and corrected the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

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