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An integrative prediction model of successful sperm retrieval for men with non-obstructive azoospermia

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Abstract

Microdissection testicular sperm extraction (micro-TESE) is an efficient method for obtaining spermatozoa from patients with non-obstructive azoospermia, but the overall success rate of this surgery is only approximately one-third. This study aimed to construct an integrative prediction model for andrologists to assess the preoperative success retrieval rate. A total of 217 patients diagnosed with non-obstructive azoospermia at the First Affiliated Hospital of Nanjing Medical University were included, in whom sperm was successfully retrieved in 71 patients. We retrospectively analyzed their clinical characteristics and pathological features. Single factor analysis and logistic regression analysis were utilized to validate the predictive performance, and the area under the curve (AUC) analysis was conducted to further assess the clinical diagnostic value of the model. The results showed that a history of Klinefelter syndrome or cryptorchidism, FSH (Follicle Stimulating Hormone) levels, and testicular pathology contributed differently to the nomogram prediction model. Relatively normal FSH levels, a history of Klinefelter syndrome or cryptorchidism, and favorable testicular pathological types were assigned higher scores, with higher scores often accompanying a preferable success rate of sperm retrieval. The integrated model showed good prediction performance, with an AUC (Area Under the Curve) of 0.781 (95% CI (confidence interval) 0.713–0.849). Overall, our integrative model demonstrates excellent prediction performance and may assist andrologists in balancing the benefits of surgery preoperatively.

Keywords

Non-obstructive azoospermia; Micro-TESE; Prediction model

Un modelo predictivo integral para el éxito de la recuperación de espermatozoides en hombres con azoospermia no obstructiva

Resumen

La microanatomía de la extracción de espermatozoides testiculares (microtese) es un método eficaz para ayudar a los andrólogos a obtener espermatozoides de pacientes con azoospermia no obstructiva. Sin embargo, la tasa general de éxito de la cirugía es de solo alrededor de un tercio. Nuestro estudio tiene como objetivo construir un modelo predictivo integral para andrólogos para evaluar la tasa de éxito preoperatorio. Nuestro estudio incluyó a un total de 217 pacientes diagnosticados con azoospermia no obstructiva en el Primer Hospital Afiliado de la Universidad Médica de nanjing, de los cuales 71 recuperaron con éxito espermatozoides. Analizamos retrospectivamente sus características clínicas y patológicas. posteriormente se utilizó un análisis univariado y un análisis de regresión logística para verificar su rendimiento predictivo. Se realizó un análisis de área bajo curva para evaluar más a fondo el valor diagnóstico clínico del modelo. Encontramos que la historia clínica del síndrome de Klinefelter o criptorquídeos, la FSH (Hormona estimulante del folículo) y la patología testicular contribuyen de manera diferente al modelo predictivo de nomograma. Los niveles relativamente normales de FSH, los antecedentes de síndrome de Klinefelter o criptorquidismo y los buenos tipos patológicos testiculares obtuvieron puntajes más altos. Las puntuaciones más altas a menudo van acompañadas de una mayor tasa de éxito en la recuperación de espermatozoides. El modelo combinado mostró un buen rendimiento predictivo, con un AUC (Área bajo curva) de 0.781 (ic (Intervalo de confianza) 95% 0.713–0.849). Nuestro modelo integral muestra un excelente rendimiento predictivo que puede ayudar a los andrólogos a equilibrar los beneficios de la cirugía preoperatoria.

Palabras Clave

Azoospermia no obstructiva; Microtese; Modelo predictivo

1. Introduction

Non-obstructive azoospermia (NOA) is characterized by the near absence of fully developed sperm in the seminiferous tubules, affecting approximately one in 100 men worldwide [1, 2]. Unlike obstructive azoospermia (OA), NOA is caused by primary or secondary testicular spermatogenic dysfunction or failure [3]. Most affected men are unable to have biological children without the use of donor sperm, and only a few can achieve biological offspring through assisted reproductive technology [4]. Although artificial sperm and autotransplantation of spermatogonial stem cells may offer future alternatives, a definitive treatment is currently unavailable [4–7]. Therefore, NOA is considered the most severe form of male infertility.

With the advancement of research and technology, microdissection testicular sperm extraction (micro-TESE) has been developed and provides new hope for the fertility of NOA patients [8]. Despite the absence of sperm in the semen, there may be focal spermatogenesis in the testicular tissue of NOA patients. Using a surgical microscope, andrologists can directly observe relatively full and opaque seminiferous tubules during the procedure, which improves the sperm acquisition rate and represents the only way for NOA patients to achieve biological children [9, 10]. Recent research indicates that the success rate of micro-TESE ranges from approximately 30% to 60% [11–13]. Some studies suggest that micro-TESE has clinical benefits over conventional TESE. Amer *et al.* [14] reported a successful retrieval rate of 47% (37%–57%) for micro-TESE, which is statistically higher than that of the traditional method. A systematic review also revealed a higher acquisition rate for micro-TESE in NOA patients, particularly those with patchy spermatogenesis [15]. However, a significant proportion of patients still fail to achieve satisfactory results after undergoing surgical trauma.

In this study, we aim to construct an integrative prediction model based on clinical features, pathological classifications, and sex hormones levels, which may assist andrologists in making better clinical decisions and minimizing unnecessary harm to patients.

2. Methods

2.1 Research object and preoperative examination

From March 2018 to December 2022, a total of 217 patients who underwent a micro-TESE operation following three or more semen examinations indicating azoospermia at the First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu, China) were included in this study. Semen analysis was conducted according to the Fifth Edition of the Semen Analysis Standards enacted by the WHO (world health organization). All included patients underwent sex hormone examination, Doppler ultrasonography, physical examination, and other necessary tests to exclude obstructive azoospermia, as well as infectious or non-infectious diseases or inflammation of the accessory glands and the reproductive tract. Chromosome karyotype analysis was also performed to confirm the diagnosis of Klinefelter syndrome (21 homozygotes and 4 mosaicism). All included patients had a confirmed diagnosis of NOA. Clinical characteristics and pathological features were retrospectively analyzed. Their data collected on the second day after admission and pathological results obtained post-surgery were used as predictors. The primary outcome measure was the successful retrieval of sperm. The sample size met the requirement of more than 10 events per variable (EPV). Only complete data were analyzed [16].

2.2 Surgical technique

Micro-TESE was performed under general anesthesia. Briefly, the patients received an intravenous dose of cefuroxime (1.5 g) before and after the operation. A mid-scrotal incision was made to access the testis through the layers of the scrotum. After dissecting the testicular parenchyma, a microscope was used to select relatively full and opaque seminiferous tubules. The selected tubules were processed by a specialist in the embryo room. The contralateral testis was treated similarly. If sperm were found, they were cryopreserved for future procedures such as intracytoplasmic sperm injection (ICSI). Additionally, a small sample of testicular tissue was taken for histopathological examination.

2.3 Histopathological examination

The testicular tissue obtained during surgery was fixed in paraformaldehyde and then embedded. Hematoxylin and eosin staining was used for histological analysis. Pathologic diagnoses were made by two pathologists and an andrologist proficient in testicular pathology. Sertoli-cell-only syndrome (SCOS) was identified by the presence of only supporting cells under the microscope. Maturation arrest (MA) was defined by the presence of spermatogenic cells at various stages and early sperm but no late sperm. Hypospermatogenesis (HS) indicated slightly altered spermatogenic function with the presence of late sperm.

2.4 Statistical analysis

Statistical analysis was performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and R software 4.2.1 (Bell Laboratories, Murray Hill, NJ, USA). Normally distributed data are expressed as mean $\pm$ standard deviation (s.d), while non-normally distributed data are expressed as median (IQR, Interquartile Range). Student's *t*-test was used to compare means of continuous variables, and the Wilcoxon rank-sum test was applied to compare ranked data with two categories. The Pearson χ^2 test was used to analyze ratios between groups. A p-value < 0.05 was considered statistically significant. A predictive model for sperm retrieval success was constructed using logistic regression analysis. The nomogram was created using the Regression Modeling Strategies package in R software (R version 4.2.1). The "pROC" package was used to draw the receiver operating characteristic (ROC) curve and calculate the AUC and 95% CI.

3. Results

3.1 Clinical characteristics of the patients and single-factor analysis

Data analysis showed that 28 of 217 patients had a history of Klinefelter syndrome (Table 1). Testicular sperm were successfully retrieved in 14 (50.0%) of these patients, compared to 57 (30.2%) of the 189 patients with a normal chromosome karyotype. Among the 25 patients with a history of cryptorchidism, the sperm retrieval rate (SRR) was higher (60.0%) compared to the 192 patients without cryptorchidism (40.0%), with a statistically significant difference ($p = 0.002$). Additionally, patients with HS exhibited a higher success rate (76.2%) compared to those with SCOS and MA, which had success rates of 14.5% and 38.1%, respectively ($p < 0.001$). High follicle-stimulating hormone (FSH) levels were associated with a lower success rate ($p = 0.013$). These results suggest that a history of Klinefelter syndrome or cryptorchidism, FSH levels, and testicular pathology could be predictive factors for SRR. Patients with relatively normal FSH levels, a history of Klinefelter syndrome or cryptorchidism, and favorable testicular pathological types had higher chances of successful sperm retrieval. No significant differences were found for AZFc (Azoospermia factor C region) microdeletion, history of hernia surgery, dominant testicular volume, luteinizing hormone (LH) levels, age, or body mass index (BMI).

3.2 Construction and validation of the prediction model

We successfully constructed a multivariate model using four factors selected by Lasso feature screening (Fig. 1) combined with logistic regression to predict the success rate of sperm retrieval (SSR) in the micro-TESE operation. The final prediction model included the history of cryptorchidism ($p < 0.001$), history of Klinefelter syndrome ($p = 0.001$), FSH level ($p = 0.006$), and testicular pathology ($p = 0.001$) (Table 2).

Using the Regression Modeling Strategies package in R software (R version 4.2.1), we constructed a nomogram as our prediction model based on logistic regression analysis of the selected factors (Fig. 2). Each variable's contribution to

TABLE 1. Clinical characteristics of the patients and single factor analysis.

	Total	Outcome		*p* value
		Success	Failure	
Age (yr), median (IQR)	30.000 (28.000–32.000)	29.000 (28.000–31.000)	30.000 (29.000–32.000)	0.152
BMI (kg/m^2), mean ± s.d	25.832 ± 1.755	25.920 ± 1.898	25.790 ± 1.686	0.611
Klinefelter syndrome, n (%)				
Positive	28 (12.9)	14 (50.0)	14 (50.0)	0.037
Negative	189 (87.1)	57 (30.2)	132 (69.8)	
AZFc microdeletion, n (%)				
Positive	10 (4.6)	6 (60.0)	4 (40.0)	0.124
Negative	207 (95.4)	65 (31.4)	142 (68.6)	
History of cryptorchidism, n (%)				
Positive	25 (11.5)	15 (60.0)	10 (40.0)	0.002
Negative	192 (88.5)	56 (29.2)	136 (70.8)	
History of hernia surgery, n (%)				
Positive	12 (5.5)	1 (8.3)	11 (91.7)	0.125
Negative	205 (94.5)	64 (31.2)	141 (68.8)	
Testicular pathology				
SCOS	83 (38.2)	12 (14.5)	71 (85.5)	<0.001
MA	113 (52.1)	43 (38.1)	70 (61.9)	
HS	21 (9.7)	16 (76.2)	5 (23.8)	
Dominant testicular volume (mL), mean ± s.d	6.560 ± 3.065	6.320 ± 2.989	6.680 ± 3.105	0.426
Testosterone (nmol/L), mean ± s.d	10.517 ± 5.250	9.549 ± 5.961	10.988 ± 4.818	0.079
FSH (IU/L), median (IQR)	14.830 (10.825–21.680)	12.900 (9.250–19.800)	16.150 (11.320–21.850)	0.013
LH (IU/L), median (IQR)	8.800 (5.865–11.400)	9.960 (6.080–13.460)	8.500 (5.710–11.400)	0.222

BMI: body mass index; s.d: standard deviation; AZFc: Azoospermia factor C region; SCOS: Sertoli-cell-only syndrome; MA: Maturation arrest; HS: Hypospermatogenesis; FSH: follicle-stimulating hormone; IQR: Interquartile Range; LH: luteinizing hormone.

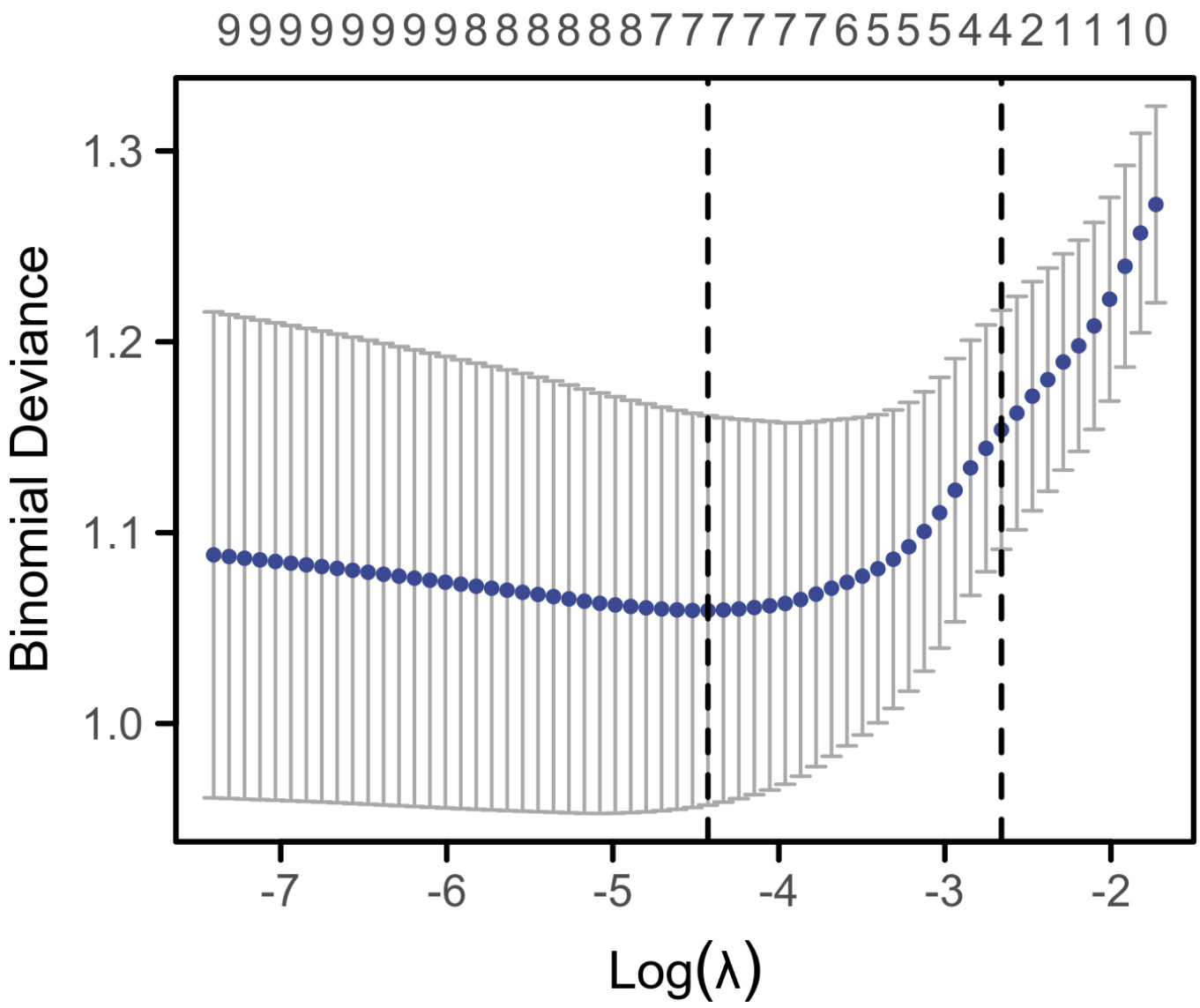

FIGURE 1. Lasso variable screening. Lasso regression was used to select the most important features. It achieves sparsity by adding a penalty term (L1 regularization) to the optimization objective function, so that the weight of many features in the coefficient vector becomes 0. By selecting the features corresponding to non-zero coefficients, the features with the greatest predictive ability for the target variables can be screened out, thereby simplifying the model and improving the generalization ability of the model. Based on different boundary values, the effective variables selected by the Lasso algorithm range from 4 to 7.

TABLE 2. Multivariate analysis of factors associated with success rate of mi-TESE.

Factor	OR	95% CI	*p* value
History of cryptorchidism	5.183	2.378–12.468	<0.001
Klinefelter syndrome	6.977	2.016–13.998	0.001
Testicular pathology			
SCOS *vs.* MA	2.656	2.138–10.761	0.001
SCOS *vs.* HS	9.703	7.174–49.516	<0.001
FSH level	0.938	0.896–0.981	0.006

OR: Odds Ratio; CI: confidence interval; SCOS: Sertoli-cell-only syndrome; MA: Maturation arrest; HS: Hypospermatogenesis; FSH: follicle-stimulating hormone.

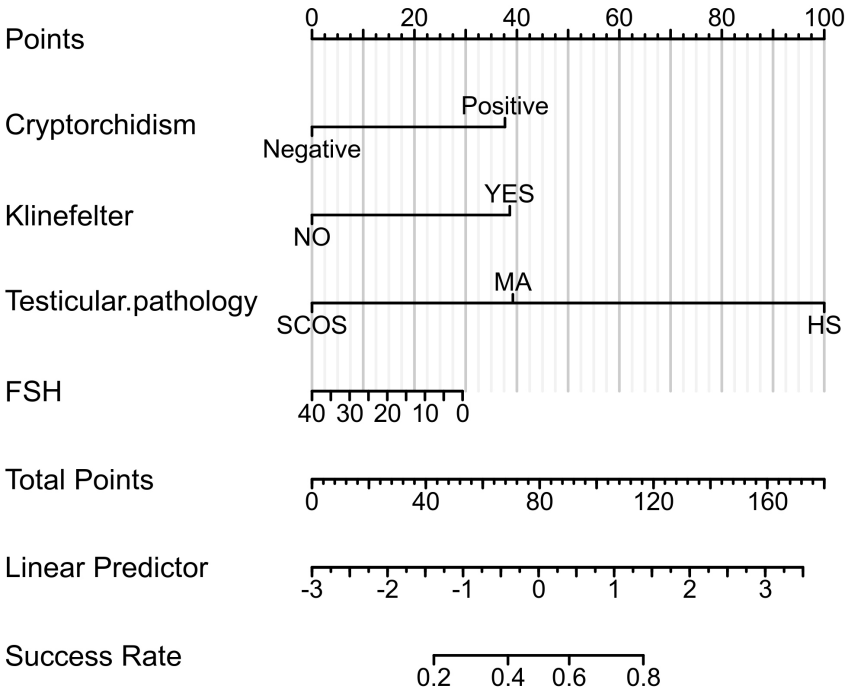

FIGURE 2. Nomogram of the integrated prediction model for a success retrieval rate of micro-TESE. The nomogram predicts the probability of successful sperm extraction in patients undergoing micro-TESE based on the history of Klinefelter syndrome or cryptorchidism, FSH level and testicular pathology. The scores corresponding to each clinical feature is at the top. Sum the points of all predictors and locate the final points on the total point axis. Finally, map the point to the "Success Rate" axis by drawing a line straight down to determine the patient's probability of successful sperm extraction. SCOS: Sertoli-cell-only syndrome; MA: Maturation arrest; HS: Hypospermatogenesis; FSH: follicle-stimulating hormone.

the overall model was assigned a corresponding score, which was mapped to the "Points" axis. The summed points of each variable, along with the corresponding final success rate of sperm retrieval, are displayed at the bottom. According to the nomogram, it is evident that patients with higher "Total Points" have a higher likelihood of successful sperm retrieval. The points for each parameter were allocated as follows: a history of cryptorchidism or Klinefelter syndrome contributed 37 or 38 points, respectively; SCOS, MA and HS contributed 0, 39 and 100 points, respectively. Higher FSH levels resulted in lower scores. For example, according to the nomogram model, a Klinefelter syndrome patient with MA testicular pathology and an FSH level of 20 IU/L, without cryptorchidism, would accumulate approximately 38 + 39 + 15 + 0 = 92 points, corresponding to a success rate of about 0.64. Additionally, the ROC and calibration curves were drawn to further evaluate the model, revealing an AUC of 0.781, with a 95% CI of 0.713–0.849 (Fig. 3).

3.3 Follow-up of pregnancy outcome

In our study, 217 NOA patients underwent micro-TESE after three or more semen examinations, which indicated azoospermia. The patients' age ranged from 23 to 42 years. Testicular sperm were successfully retrieved in 71 of the 217 patients, resulting in an SRR of 32.7%. These samples were cryopreserved in the sperm bank of Jiangsu Province for future reproductive procedures.

As of December 2023, 42 couples had undergone ICSI. The age of the males ranged from 24 to 38 years, and the age of the females ranged from 21 to 36 years. A total of 63 oocyte retrieval cycles and 47 ICSI cycles were completed. The average numbers of 2PN (pronucleus), 2PN cleavage, transferable embryos, and high-quality embryos are shown in Table 3. There were 25 cases of pregnancy, 10 cases of childbirth, and 9 cases of spontaneous abortion. The outcomes of ICSI in the 42 couples are illustrated in Fig. 4.

TABLE 3. Outcomes of ICSI in the 42 spouses of the non-obstructive azoospermia patients undergoing micro-TESE.

Variable	Total (mean)
2PN	2–12 (5.5)
2PN cleavage	2–11 (5.1)
Transplantable embryos	2–8 (5.0)
High-quality embryos	1–7 (3.1)
Clinical pregnancy (frozen embryo transfer)	20
Clinical pregnancy (fresh transfer)	5
Spontaneous abortion	9
Live birth	10

PN: pronucleus.

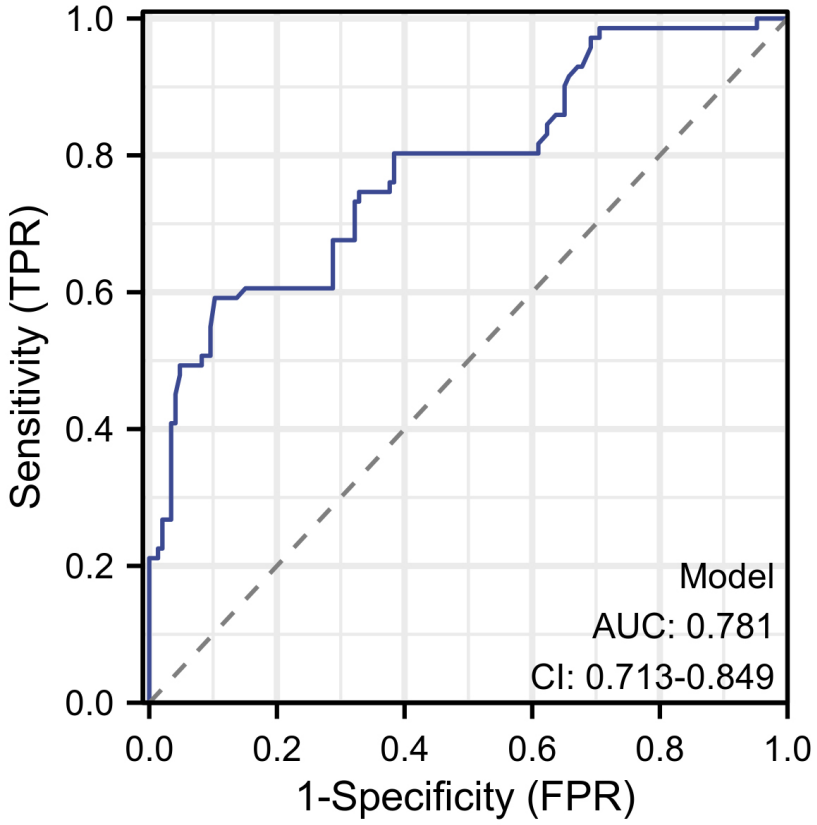

FIGURE 3. The ROC curve of the success retrieval rate prediction model. ROC (Receiver Operating Characteristic) curve of the nomogram for successful sperm extraction rate of prediction model. The solid line represents the ability of the prediction model discriminating the actual successful sperm retrieval patients from the failed ones. More closer to the (0,1) means a better performance for the curve. AUC (Area Under the Curve) for ROC curve is 0.781 (95% CI (confidence interval) 0.713–0.849). TPR: true positive rate; FPR: false positive rate.

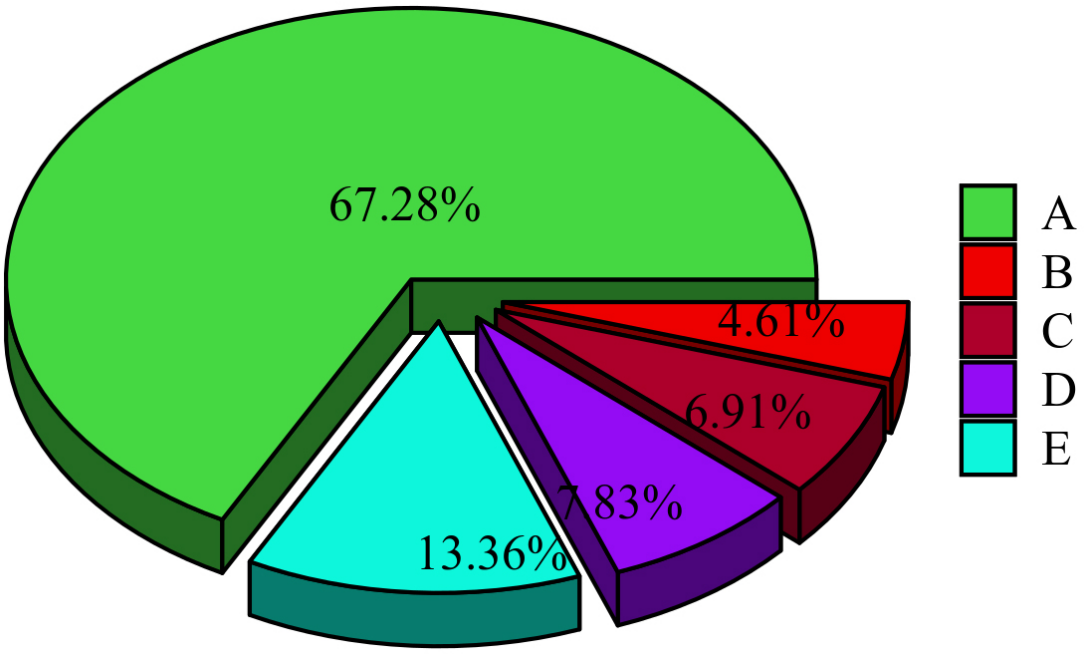

FIGURE 4. Pie chart of outcomes of ICSI in the 42 spouses of NOA patients. The outcome of ICSI in the 42 spouses of NOA patients was followed up regularly till December 2023 and finally presented in the form of pie chart. The meanings of each part are as follows: (A) NOA patients with unsuccessful outcomes. (B + C + D + E) NOA patients with successful outcomes. (C + D + E) Total ICSI cycles in the 42 spouses. (D + E) Clinical pregnancies. (E) Live births.

4. Discussion

To the best of our knowledge, this is one of the few studies to construct an integrative prediction model for successful sperm retrieval in men with NOA and to continuously follow up on pregnancy outcomes. By analyzing data from 217 patients, we found that a history of Klinefelter syndrome or cryptorchidism, FSH levels, and testicular pathology are crucial factors affecting the success rate of micro-TESE.

Klinefelter syndrome (KS) is the most frequent sex chromosome abnormality [17] and is a major cause of NOA [18]. Although its prevalence ranges from 1:500 to 1:700 in newborn males, it is commonly underdiagnosed [19]. For KS patients, the fertility rate is gradually increasing with the development of advanced assisted reproductive techniques, particularly micro-TESE. Aksglaede *et al*. [20] reported an average SRR of 57% using micro-TESE in a study of 741 males with KS. Sabbaghian *et al*. [21] found that after micro-TESE, the fertilization rate, pregnancy rate, and live birth rate were higher in the KS group than in men with NOA. However, Kocamanoglu *et al*. [22] identified that the SRR of KS patients is lower than that of NOA patients after the age of 31.5. Guo *et al*. [23] reported that higher preoperative testosterone (T) levels are associated with a greater likelihood of successful sperm recovery in KS patients. However, our research showed that T and LH levels did not affect the outcome of micro-TESE in the multivariate regression model, consistent with the findings of a meta-analysis conducted by Corona *et al*. [12]. They did not observe an association between FSH and SRR, whereas our research indicated that high FSH levels were associated with worse outcomes. The differences in research results may be due to the limitations of single-center studies and insufficient sample sizes. Clinically, we observed that higher FSH levels tend to be associated with poor sperm retrieval outcomes, suggesting that higher FSH may signal spermatogenic failure, which requires further investigation. In the multivariate analysis model, testicular pathological types more accurately reflected testicular spermatogenesis, thereby weakening the role of FSH in subsequent regression analysis.

Cryptorchidism is the most common congenital urogenital malformation in boys, with an incidence of approximately 2%–5% in newborns [24]. Previous research has linked cryptorchidism to hypospadias, impaired fertility, and testicular cancer [25]. Chung *et al*. [26] proposed that incorrect testicular positioning and hormone imbalances are causes of infertility in individuals with cryptorchidism. Orchidopexy is the primary therapeutic strategy, and some studies have shown that hormones such as gonadotropin-releasing hormone (GnRH) are more effective when used in combination with surgery [27]. Virtanen *et al*. [28] reported that 28% of adults with bilateral cryptorchidism had normal sperm counts after the operation, and patients with unilateral cryptorchidism tend to have higher sperm quality than those with bilateral cryptorchidism. Chen *et al*. [29] found that the success rate of micro-TESE in unilateral/low-positional cryptorchidism was higher than in bilateral/high-positional cryptorchidism. Sangster *et al*. [30] revealed that micro-TESE following orchidopexy for inguinal testicles resulted in a successful SRR in over one-third of patients. Collectively, these findings are consistent with the results of our present study.

Previous research has revealed a relationship between testicular histopathology and SRR [31]. However, these studies focused only on patients with Klinefelter syndrome or idiopathic NOA [32, 33]. Herein, our investigation extended this to a wider population, revealing a relationship between testicular histopathology and various types of NOA. Additionally, several studies have examined the relationship between the pathological types of testicular tissues and specific RNA expression. High expression of hsa_circ_0000116 has been associated with a worsened SRR, especially in SCOS patients [34, 35], suggesting that circRNAs may play different roles in different pathological types of NOA. Therefore, determining the plasma or seminal circRNA content preoperatively could potentially indicate the surgical outcome.

It is important to consider whether biopsy puncture or direct microscopic sperm extraction should be the initial approach for NOA. Currently, the sperm retrieval rate for microdissection ranges from 43% to 63% [36], approximately 20% higher than that of biopsy. However, no effective method exists to predict the sperm retrieval rate for either microdissection or conventional biopsy. Meta-analyses suggest that previous sperm retrieval outcomes and pathological analyses provide the only relatively valuable information for prediction [37, 38]. Given the lack of effective non-surgical sperm retrieval methods for NOA, drug treatment outcomes are largely disappointing. Consequently, some scholars recommend that micro-TESE be performed whenever possible, rather than other methods with lower sperm retrieval rates, such as puncture or testicular incision biopsy.

Based on our clinical experience, it can be suggested that NOA caused by cryptorchidism has a relatively high rate of sperm extraction with micro-TESE, while conventional biopsy yields lower rates, making micro-TESE the more suitable approach. For NOA associated with Klinefelter syndrome or severe testicular dysplasia, the testes are typically small and difficult to puncture, often accompanied by Leydig cell proliferation and severe hyalinization of the seminiferous tubules, making it challenging to extract seminiferous tubules and results in minimal tissue yield. Therefore, micro-TESE is the first choice for these cases. For patients with idiopathic NOA and relatively normal testicular volume, it may be worth discussing whether a biopsy should be attempted first to compare sperm retrieval rates with microdissection.

In this present research, we analyzed clinical features and sex hormone levels alongside testicular pathology to build a comprehensive prediction model and concluded that relatively normal FSH levels, a history of Klinefelter syndrome or cryptorchidism, and testicular pathological types of MA or HS are more likely to result in successful sperm extraction. The excellent predictive performance of our model was confirmed using an ROC curve. Although micro-TESE has a success rate of about one-third, the subsequent ICSI rate is less than 60%, and the final live birth rate is less than 10%. Thus, assisted reproduction still faces significant challenges.

Our study had some limitations that should be considered. First, the small sample size necessitates further testing in larger cohorts to reduce bias. Second, as a single-center retrospective study, the reliability of our results may be limited.

We plan to conduct a prospective study to validate our findings. Additionally, further investigations are needed on the impact of circRNAs on spermatogenesis and their role in azoospermia in greater detail, including mechanistic research. However, it should also be noted that our present study is one of the few studies to construct an integrative prediction model for successful sperm retrieval in men with NOA and to continuously follow up on pregnancy outcomes.

5. Conclusions

In conclusion, our research comprehensively included testicular pathology features, clinical features, and sex hormone levels to construct an integrative prediction model of SRR for NOA patients. We found that a history of Klinefelter syndrome or cryptorchidism, FSH level, and testicular pathology are crucial factors affecting the success rate of micro-TESE operations. Relatively normal FSH levels, a history of Klinefelter syndrome or cryptorchidism, and testicular pathological types of MA or HS were more likely to result in successful sperm extraction. The comprehensive model demonstrated good predictive performance, with an AUC of 0.781 (95% CI 0.713–0.849), and could help andrologists make better clinical decisions and avoid unnecessary injury to NOA patients.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

ZPL and XCX—designed the research study. XCX, YCW and CY—performed the research. CQ and WW—provided help and advice on the improvement of the study; provided administrative support and revised the manuscript. ZPL—analyzed the data. XCX—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research was conducted in accordance with the guidelines of the Declaration of Helsinki (as revised in 2013) and adhered to the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. The study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No: 2018-SRFA-035), and all patients provided informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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