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Original Article

Development of a predictive nomogram for microscopic inferior epigastric vein-internal spermatic vein surgery in male infertility with combined varicocele and nutcracker syndrome

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Abstract: Objective: To construct a microscopic inferior epigastric vein-internal spermatic vein model based on testis-related indexes in infertile men with asthenospermia for predictingtreatment efficacy. Methods: A total of 264 male infertile patients with oligoasthenospermia and varicocele combined with nutcracker syndrome who received treatment of the inferior epigastric-internal spermatic vein under the microscope were collected and retrospectively analyzed. They were divided into a training set (n = 185) and a verification set (n = 79). Demographic characteristics of the patients and testicular-related indicators were collected. Univariate and multivariate analyses were used to screen for risk factors affecting the surgical effect, and a predictive model was constructed. The nomogram was drawn and its clinical application value was evaluated. Results: Multivariate logistic regression analysis showed that testicular volume, sperm motility, testicular artery blood flow velocity, testosterone level, the degree of varicocele, and the severity of nutcracker syndrome were independent risk factors for the surgical outcome. The constructed predictive model performed well in the training set and the verification set, with the C-index being 0.849 and 0.847, respectively. Decision curve analysis showed that the model had clinical application value within a certain threshold probability range. The prognostic model displayed strong discrimination performance, as evidenced by external validation. Conclusion: The predictive model and nomogram constructed based on testis-related indicators are valuable for evaluating the therapeutic effect of inferior epigastric-internal spermatic vein surgery under the microscope, and also helpful for clinicians to predict the surgical effect and formulate an individualized treatment plan.

Keywords: Asthenospermic infertility, varicocele, nutcracker syndrome, predictive model

Introduction

Varicocele is one of the common causes of male infertility. Patients with oligospermia-type varicocele not only have the varicocele abnormality, but also have the problem of reduced sperm count and motility, which seriously affects fertility [1]. At the same time, nutcracker syndrome is not uncommon in patients with varicocele, which can lead to compression of the left renal vein, further affecting the return of the spermatic vein. This aggravates the pathologic changes to the testis and complicates the male infertility [2].

Microscopic inferior epigastric vein-internal spermatic vein surgery is an effective surgical method for the treatment of male infertility and oligoasthenospermia-type varicocele combined with nutcracker. By establishing a new venous return channel, it can promote the blood circulation of spermatic vein and testis, theoretically improve the sperm quality, and restore fertility [3]. However, clinical practice has revealed that treatment outcomes vary significantly among patients undergoing this procedure. While some patients experience marked improvement in semen quality and fertility post-surgery, others show poor surgical results with no noticeable enhancement of semen quality, and their fertility issues remain unresolved [4].

At present, factors affecting the therapeutic effect of microscopic inferior epigastric vein-internal spermatic vein surgery are still unclear, and there is a lack of effective predictive meth-

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ods and tools. It is difficult for clinicians to evaluate accurately the surgical outcomes in patients, and also unable to provide patients with accurate treatment recommendations and personalized treatment options [5]. This not only affects patients' confidence during treatment, but also limits the clinical application and promotion of this surgery to some extent. Therefore, exploring relevant factors affecting the effect of surgical treatment, building prediction models, and drawing nomograms are of great clinical significance for improving the accuracy of surgical treatment.

Subjects and methods

Subjects

Clinical files of 264 infertile men with oligospermia and varicocele combined with nutcracker syndrome were selected and retrospectively analyzed. Patients received treatment to the inferior epigastric vein-internal spermatic vein under the microscope at Ganzhou People's Hospital from January 2022 to January 2024. Inclusion criteria: confirmed diagnosis of varicocele (clinical grade II-III) combined with nutcracker syndrome through physical examination and color Doppler ultrasound; confirmed oligospermia through semen analysis (sperm concentration less than 15×10^6/mL, and percentage of forward moving sperm less than 32%); 18-45 years. Exclusion criteria: other diseases seriously affecting the reproductive function (such as congenital testicular agenesis, duct obstruction of vas deferens, and epididymitis); severe heart, liver, kidney, or other vital organ dysfunctions; treatment affecting the semen quality (such as hormone treatment, radiotherapy, and chemotherapy) in the past three months; infertility definitively caused by abnormal karyotype or microdeletion of Y chromosome.

According to the improvement status of semen quality six months after surgery and the pregnancy status of the patient's spouse, the patients were divided into a good operative effect group and the bad operation effect group. A good surgical outcome was defined as one that semen quality was markedly improved (increased sperm concentration by more than 50% and percentage of forward moving sperm by more than 30%) and that the patient's spouse became pregnant spontaneously or successfully through assisted reproductive technology within 12 months after surgery. Poor surgical outcome was defined as either an insignificant improvement in semen quality (increased sperm concentration by less than 50% and percentage of forward moving sperm by less than 30%) or the failure of the patient's spouse to become pregnant within 12 months after surgery.

For the external validation cohort, 104 infertile patients with asthenospermia, who were admitted to Ganzhou People's Hospital from March 2024 to December 2024 and diagnosed with nutcracker syndrome complicated by varicocele, were recruited. These patients were scheduled to undergo a microscopic surgical intervention for the lower/upper abdominal veins and internal spermatic vein. The inclusion and exclusion criteria remained consistent with those mentioned earlier. Before the treatment, each patient's prognosis was evaluated using the nomogram to get the predicted risk scores. The patients were categorized into two groups (favorable vs. unfavorable outcome groups) according to the semen quality changes at 6 months after surgery and whether their spouses had conceived. The standard for favorable outcomes was as defined in the previous paragraph. This study was approved by the Ethics Committee of Ganzhou People's Hospital.

Methods

Data collection: General data of the patients were collected through electronic medical record, including age, height and weight, and body mass index (BMI).The course of the disease was recorded. Testicular hemodynamic indexes such as testicular volume, testicular artery blood flow velocity, and resistance index were measured by color Doppler ultrasound. Preoperative semen quality indexes including sperm concentration, viability (percentage of forward moving sperm), and deformity rates were collected. Preoperative sex hormone levels such as testosterone, follicle-stimulating hormone, and luteinizing hormone were measured. Karyotype analysis and Y chromosome microdeletion detection were performed, and antisperm antibody was detected. The degree of varicocele (grade II-III) according to clinical physical examination and ultrasound and the severity of nutcracker syndrome (mild, moderate or severe) according to the degree of compression of the left renal vein and collateral circulation, were evaluated.

Model building: A single factor analysis of clinical features was used to screen the possible factors affecting the surgical effect, and the factors $P<0.2$ were included in the multi-factor logistic regression model to screen the independent risk factors. A predictive model was constructed based on the results of multivariate logistic regression. The nomogram was drawn using the R software "rms" package to score each independent risk factor, and the total score for predicting the unsatisfactory effect of surgery was calculated. Therefore, the prediction probability reflected the output result of the model.

Model evaluation and verification: 264 patients were randomized into a training set (n = 185) and a verification set (n = 79). Receiver operating characteristic (ROC) curve was drawn in the training set to calculate the area under the curve (AUC) and evaluate the predictive accuracy of the model. The calibration curve was drawn to assess the consistency of the prediction probability of the model with the actual observation results. The goodness of fit of the model was evaluated using Hosmer-Lemeshow test. The model was internally validated in the verification set, and the C-index index was calculated to evaluate the model's distinguishing ability. At the same time, a decision curve analysis (DCA) was used to evaluate the clinical application value of the model and determine the net benefit of poor surgical results, as predicted by the model, under different threshold probabilities.

In the external validation phase, ROC curve analysis served as the method to evaluate the prognostic model's accuracy.

Statistical analysis

The sample size during the development phase was based on a minimum ratio of 1:10 between the number of events and predictors in the multivariate model. Therefore, a model with 17 predictors required at least 170 events. The validation set sample size was calculated based on an 80% correct answer rate (true positives and true negatives), 5% absolute error, and 5% significance level. The calculated sample size was 240 patients. Considering a 10% information loss rate, it was decided to enroll at least 264 patients at this stage. Patients were divided into a training set (n = 185) and a verification set (n = 79) according to a 7:3 scale.

SPSS 26.0 statistical software and R language 4.0.3 software were used for data analysis. When the measured data conformed to the normal distribution, they were expressed as ($\bar{x}\pm s$); the comparison between groups was examined by independent sample t test. When the data did not conform to the normal distribution, they were expressed as M (Q1, Q3); the comparison between groups was subject to a Mann-Whitney U test. Enumerated data were expressed as case number (n) and percentage (%), and intergroup comparison was performed using χ^2 test or Fisher exact probability method. Independent risk factors were screened by multi-factor logistic regression analysis, and a difference with $P<0.05$ was significant. The ROC curve was drawn with the "pROC" package, calibration curve with "ggplot2" package, and DCA with "DCA" package.

Results

Comparison of general clinical characteristics of patients between the two groups

There were 52 cases (28.22%) with poor surgical effect in the training set, and 22 cases (27.97%) in the verification set. There was no significant difference in general clinical characteristics (such as age and BMI) or most laboratory indexes between the two groups (all $P>0.05$), as shown in **Table 1**.

Univariate analysis of surgical effects

Univariate analysis showed that testicular volume, testicular arterial blood flow velocity, flow resistance index, sperm concentration, sperm motility, sperm deformity rate, testosterone level, luteinizing hormone level, varicocele severity, and nutcracker syndrome severity were associated with the poor surgical results (all $P<0.05$), as shown in **Table 2**.

Multivariate analysis of surgical effects

A poor surgical effect was taken as the dependent variable (0 = no, 1 = yes), and the factor $P<0.05$ in the univariate analysis was taken as the covariate for further multivariate logistic

Table 1. Comparison of general clinical characteristics of patients between the training set and verification set

Index	Training set (n = 185)	Validation set (n = 79)	Statistical value	*P* value
Age (years)	28.53±5.23	29.03±5.52	0.699	0.484
BMI (kg/m^2)	24.25±3.17	24.32±3.56	0.148	0.882
Course of disease (years)	4.21±1.35	4.56±1.85	1.717	0.087
Testicular volume (mL)	18.34±3.21	17.58±2.57	1.864	0.063
Testicular arterial blood flow velocity (cm/s)	25.21±5.14	24.14±4.54	1.602	0.110
Resistance index	0.68±0.18	0.73±0.24	1.862	0.063
Sperm concentration (×10/mL)	10.52±3.21	9.76±2.78	1.831	0.068
Sperm motility (%)	25.56±5.06	24.75±4.21	1.249	0.212
Sperm deformity rate (%)	39.75±5.23	41.35±8.23	1.897	0.058
Testosterone (nmol/L)	15.34±3.25	14.53±2.58	1.965	0.050
Follicle stimulating hormone (IU/L)	5.98±1.23	6.32±1.53	1.907	0.057
Luteinizing hormone (IU/L)	4.52±1.35	4.83±1.57	1.648	0.100
Chromosome karyotype abnormality (yes/no, case)	13/172	5/74	3.367	0.066
Y chromosome microdeletion (yes/no, case)	9/176	3/76	0.003	0.953
Positive antisperm antibody (yes/no, case)	21/164	11/68	0.344	0.557
Degree of varicocele (II/III degree, case)	122/63	48/31	0.649	0.420
Nutcracker syndrome severity (mild/moderate/severe, case)	92/59/34	34/26/19	0.142	0.491

Note: BMI: body mass index.

Table 2. Univariate analysis of surgical effects

Index	Group with good operation effect (n = 133)	Group with poor operation effect (n = 52)	Statistical value	*P* value
Age (years)	28.25±5.21	29.13±5.35	1.025	0.306
BMI (kg/m^2)	23.56±3.14	24.23±3.45	1.268	0.206
Course of disease (years)	3.98±1.23	4.35±1.82	1.893	0.112
Testicular volume (mL)	18.21±3.56	15.34±2.58	2.636	0.009
Testicular arterial blood flow velocity (cm/s)	25.31±5.26	22.78±4.35	3.079	0.002
Resistance index	0.68±0.12	0.75±0.26	2.503	0.013
Sperm concentration (×10/mL)	10.21±3.57	8.61±2.31	2.993	0.003
Sperm motility (%)	25.04±5.15	23.26±4.31	2.207	0.028
Sperm deformity rate (%)	38.25±5.36	40.21±4.75	2.305	0.022
Testosterone (nmol/L)	15.32±3.14	13.78±2.85	3.075	0.002
Follicle stimulating hormone (IU/L)	5.54±1.02	5.76±1.52	1.139	0.256
Luteinizing hormone (IU/L)	4.21±1.32	4.67±1.45	2.071	0.039
Chromosome karyotype abnormality (yes/no, case)	7/126	6/46	1.395	0.237
Y chromosome microdeletion (yes/no, case)	5/128	4/48	0.544	0.461
Positive antisperm antibody (yes/no, case)	12/121	9/43	2.550	0.110
Degree of varicocele (II/III degree, case)	95/38	27/25	6.334	0.011
Nutcracker syndrome severity (mild/moderate/severe, case)	78/38/17	14/21/17	12.250	0.002

Note: BMI: body mass index.

regression analysis (see **Table 3** for variable assignment). The results showed that testicular volume, sperm motility, testicular arterial blood flow velocity, testosterone level, the degree of varicocele, and the severity of nutcracker syndrome were independent risk factors for

Table 3. Variable assignment

Variable	Meaning	Evaluation
X1	Testicular volume	continuous variable
X2	Testicular arterial blood flow velocity	continuous variable
X3	Sperm motility	continuous variable
X4	Testosterone	continuous variable
X5	Degree of varicocele	II degree = 1, III degree = 2
X6	Severity of nutcracker syndrome	Mild = 0, moderate = 1, severe = 2
Y	The operation had poor results	Poor surgical effect = 1, good surgical effect = 0

Table 4. Multivariate analysis of poor clinical effect in training set

Factor	*B*	Standard error	*Wald*	*P*	*OR*	95% confidence interval
Testicular volume	-0.314	0.071	19.723	0.001	0.731	0.636-0.839
Testicular arterial blood flow velocity	-0.081	0.041	3.864	0.049	0.922	0.851-1.000
Sperm motility	-0.096	0.042	5.290	0.021	0.909	0.837-0.986
Testosterone	-0.198	0.072	7.672	0.006	0.820	0.713-0.944
Degree of varicocele	1.811	0.709	6.516	0.011	6.114	1.523-24.550
Severity of nutcracker syndrome	1.755	0.443	15.687	0.001	5.786	2.427-13.792
constant	8.921	2.199	16.453	0.001	7484.437	

Note: OR: odds ratio.

the surgical effect (all P<0.05), as shown in **Table 4**.

Construction of a nomogram model

The nomogram model was constructed based on the independent risk factors identified by multivariate logistic regression analysis. In the model, independent risk factors such as testicular volume, sperm motility, testicular artery blood flow velocity, testosterone level, degree of varicocele, and severity of nutcracker syndrome were scored, and the total score was calculated based on the actual values of various indicators of patients, thereby predicting the probability of poor surgical results. A higher overall score indicated a higher probability of predicting poor surgical outcomes, as shown in **Figure 1**.

ROC curves and calibration curve analyses

In the training and verification sets, the C-index of the nomogram model was 0.849 and 0.847, respectively. The calibration curve showed that the predicted value accorded well with the true value. The results of Hosmer-Lemeshow test were χ = 8.778, P = 0.361 and χ^2 = 12.929, P = 0.114, respectively. The ROC curves were presented in the training and validation sets. The nomogram model predicted the AUC values of 0.848 (95% confidence interval [CI]: 0.778-0.917) and 0.833 (95% CI: 0.723-0.944) in both groups, with sensitivity and specificity of 0.750, 0.851 and 0.562, 0.795, respectively. The calibration curve is shown in **Figure 2** and the ROC curve is shown in **Figure 3**.

DCA of the nomogram model

Analysis of a decision curve showed that when the threshold probability was within the range of 0.08-0.95, the decision to apply this nomogram model was more clinically beneficial than a blanket approach of categorizing all patients based on efficacy, as shown in **Figure 4**.

Analysis of the external validation cohort

In the external validation cohort, a favorable outcome was observed in 75 cases (72.12%), with a mean age of 29.34±6.13 years. The remaining 29 cases (27.88%), demonstrating unfavorable outcomes, had an average age of 30.15±5.79 years. As presented in **Table 5**, no significant differences were observed between groups regarding age, BMI, or disease duration (all P>0.05). Nevertheless, significant dif-

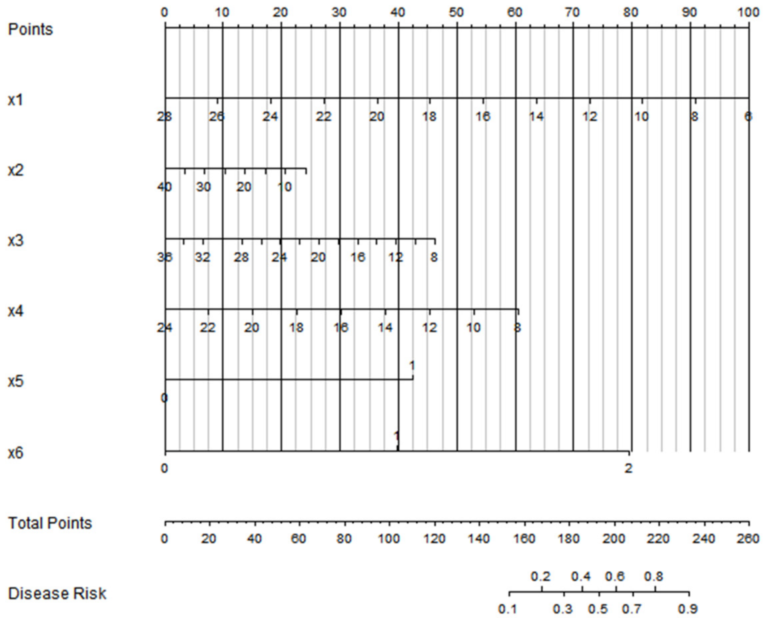

Figure 1. A nomogram for predicting treatment efficacy in oligospermic men with varicocele and nutcracker. Note: x1: testicular volume; x2: testicular artery blood flow velocity; x3: sperm activity; x4: testosterone; x5: degree of varicocele; x6: nutcracker syndrome severity.

ferences were noted in terms of testicular arterial blood flow velocity, and resistance index (both $P<0.05$). According to the ROC curve results (**Figure 5**), the prognostic model had a strong ability to distinguish outcomes, with an AUC of 0.818 (95% CI: 0.717-0.919).

Discussion

Varicocele combined with nutcracker syndrome is not rare in male infertility patients. The combined effect of the two seriously affects the spermatogenic function of the testis, resulting in decreased male fertility. Microscopic inferior epigastric vein-internal spermatic vein surgery is an important means for the treatment of these diseases, aiming to improve the blood circulation of spermatic vein and testis, restore the normal function of testis, and improve the quality of semen, thereby increasing the patient's reproductive potential [6]. However, the current clinical situation is that the therapeutic effect of this surgery varies significantly among different patients [7]. In some patients, the semen quality was significantly improved after surgery, and fertility was successfully achieved. However, there were also quite a number of patients with unsatisfactory surgical results and the problem of fertility has not been effectively resolved. In this study, a multivariate logistic regression analysis was used to determine that testicular volume, sperm activity, testicular artery blood flow velocity, testosterone level, the degree of varicocele, and the severity of nutcracker syndrome were independent risk factors for the surgical results.

Testicular volume is an important morphologic indicator reflecting testicular function. A smaller testicular volume often means the number of spermatogenic cells in the testis is decreased and the spermatogenic function is damaged [8]. In this study, the testicular volume of the poorly operated patients was significantly smaller than that of the well operated patients, which was consistent with previous studies. For example, studies have shown a positive correlation between testicular volume and the number of spermatogenesis. With every 1 mL reduction in testicular volume, the number of spermatogenesis may be reduced by about 10%, further confirming the importance of testicular volume in assessing the efficacy of surgery [9].

Sperm motility is one of the key indicators to measure the quality of semen and is directly related to the fertilization ability of sperm. Low sperm motility can significantly reduce the possibility of pregnancy. Even if the operation is successful in improving the blood circulation of the spermatic vein and testis, the operative effect will be greatly reduced if the sperm motility is not effectively improved [10]. The results of this study showed that the sperm viability of the group with good surgical effect was significantly higher than that of the group with poor surgical effect, indicating that sperm viability was a key factor affecting the surgical effect. Clinical studies have found that when the sperm motility increases by 10%, the probability of natural conception may increase by about 20%, which fully reflects the important effect of sperm motility on reproductive outcomes [11].

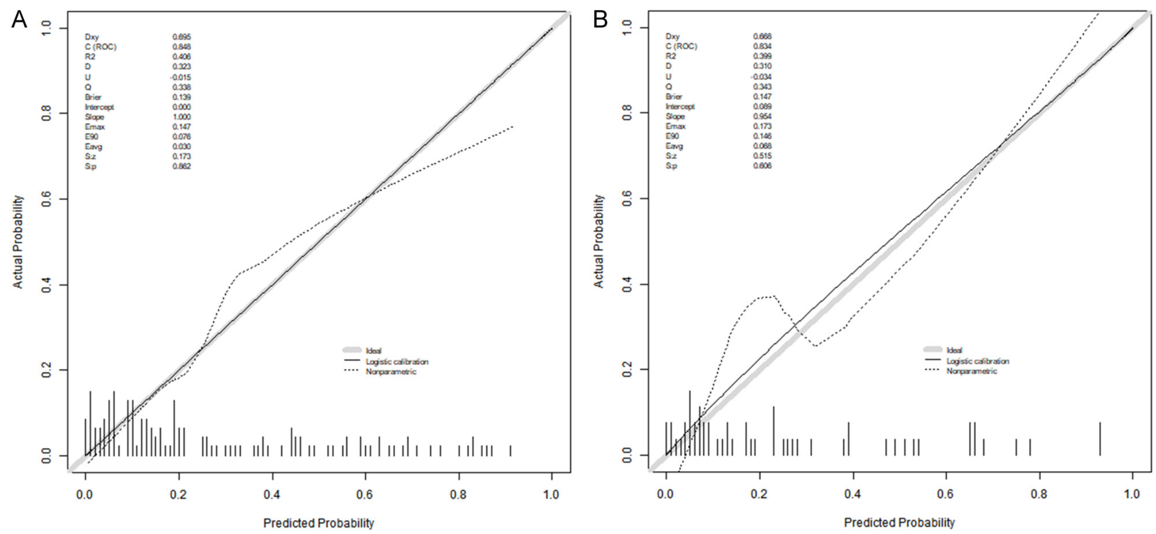

Figure 2. Calibration curve (A is the training set, and B is the verification set).

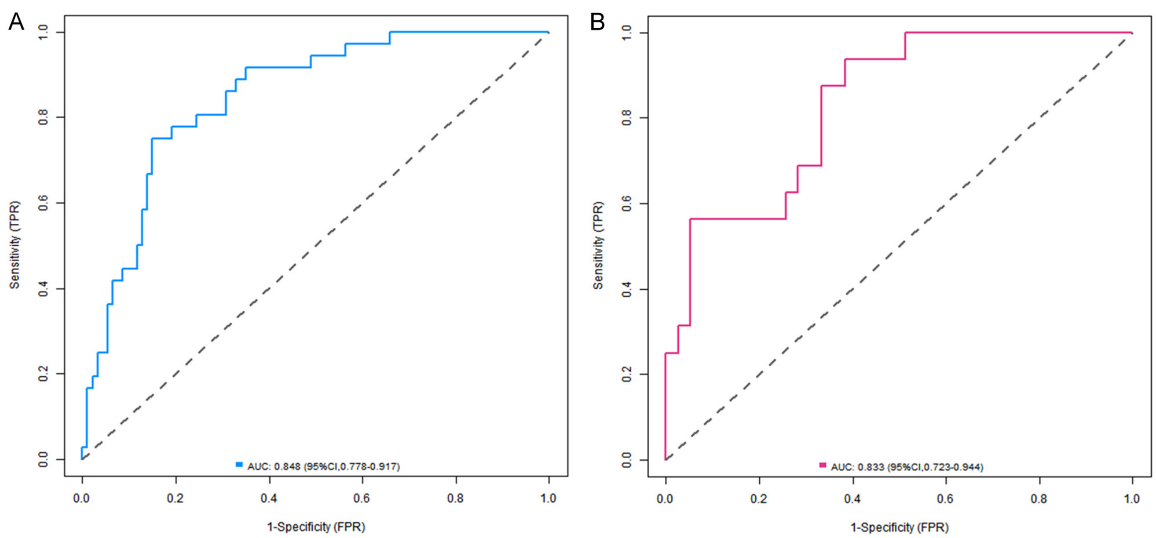

Figure 3. ROC curve (A is the training set, and B is the verification set). Note: ROC: receiver operating characteristic; CI: confidence interval; FPR: false positive rate; TPR: true positive rate.

Testicular arterial blood flow velocity reflects the blood perfusion of the testis. Good blood supply is the basis for maintaining the normal physiological function of the testis. Slow blood flow will lead to testicular ischemia and hypoxia, affecting the spermatogenic process and endocrine function of the testis [12]. In this study, the blood flow velocity of the testicular artery in the group with good surgical effect was relatively fast, indicating that adequate blood supply helped improve testicular function and the surgical effect. Studies have pointed out that for every 1 cm/s increase in testicular arterial blood flow velocity which may be increased by about 15%, which further supports the importance of testicular arterial blood flow velocity in the prediction of surgical results [13].

Testosterone plays a vital role in maintaining the spermatogenic function and reproductive metabolism of the testis [14]. Decreased testosterone levels affect sperm production, maturation and motility. In this study, testosterone levels were low in the suboptimal group, suggesting that testosterone levels were closely related to surgical outcome. Supplementing exogenous testosterone can improve the quali-

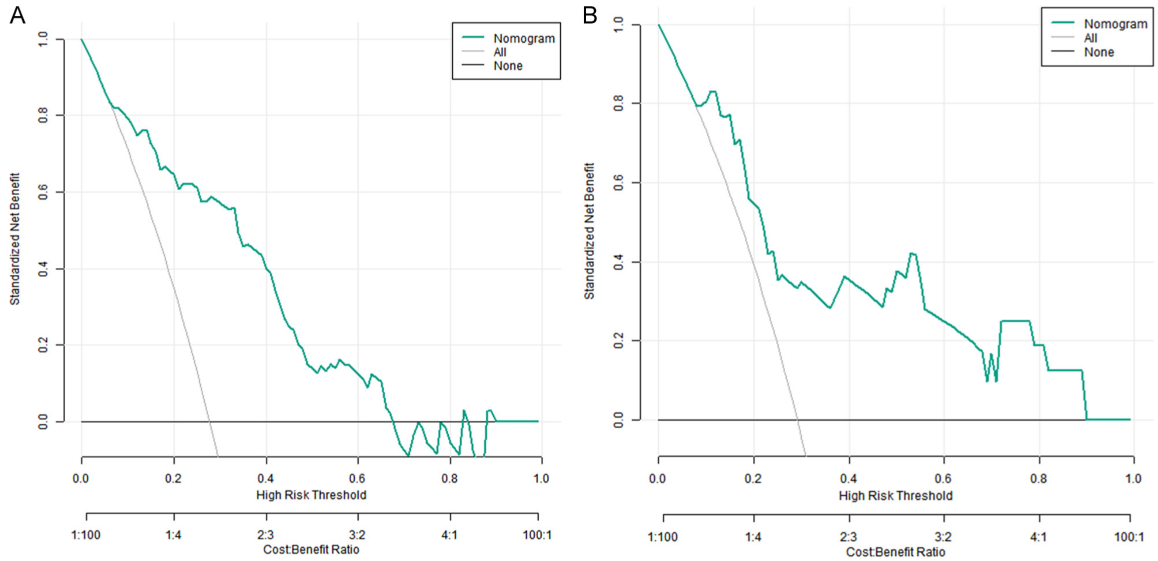

Figure 4. Decision curve (A is the training set, and B is the verification set).

Table 5. Comparison of baseline data in the external validation cohort

Index	Favorable outcome group (n = 75)	Unfavorable outcome group (n = 29)	Statistic value	*P* value
Age (years)	29.34±6.13	30.15±5.79	0.598	0.556
Body mass index (kg/m^2)	22.71±3.22	21.95±2.67	1.129	0.262
Course of disease (years)	4.12±1.35	3.93±1.33	0.644	0.521
Testicular volume (mL)	17.86±4.01	15.41±3.79	2.836	0.005
Testicular arterial blood flow velocity (cm/s)	26.12±5.98	22.43±5.01	2.945	0.040
Resistance index	0.61±0.13	0.73±0.19	3.686	0.000
Sperm concentration (×10/mL)	10.36±3.86	8.32±2.96	2.566	0.012
Sperm motility (%)	24.41±5.14	22.18±4.32	2.069	0.041
Sperm deformity rate (%)	37.54±5.96	40.48±4.91	2.604	0.011
Testosterone (nmol/L)	16.68±3.47	13.97±3.07	3.683	0.000
Follicle stimulating hormone (IU/L)	5.64±1.13	5.92±1.32	1.080	0.283
Luteinizing hormone (IU/L)	4.14±1.55	4.92±1.59	2.285	0.024
Chromosome karyotype abnormality (yes/no, case)	6/69	4/25	0.808	0.369
Y chromosome microdeletion (yes/no, case)	8/67	5/24	0.827	0.363
Positive antisperm antibody (yes/no, case)	9/66	6/23	1.279	0.258
Degree of varicocele (II/III degree, case)	53/22	17/12	1.379	0.240
Nutcracker syndrome severity (mild/moderate/severe, case)	36/28/11	16/7/6	0.646	0.724

ty and quantity of sperm to a certain extent, and also improve the reproductive outcome, which also reflects the value of testosterone in the prediction of surgical effects [15].

The degree of varicocele and the severity of nutcracker syndrome directly affect the blood return in the spermatic vein and testis. The two are important factors leading to impaired testicular function [16]. Severe varicocele and nutcracker syndrome can cause long-term congestion of testis and affect spermatogenic and endocrine functions [17]. The results of this study showed that the varicocele and nutcracker syndrome were more severe in the group with poor surgical results, indicating that the effects of these two factors on the surgical results should not be ignored. Studies have

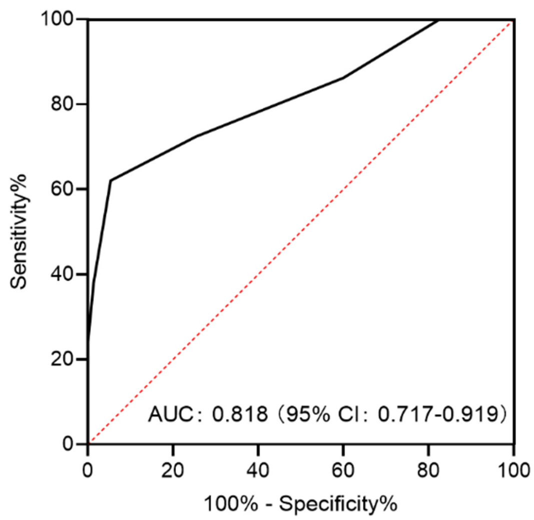

Figure 5. ROC analysis of the external verification cohort. Note: ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval.

shown that for each exacerbation of varicocele, the risk of impaired testicular spermatogenic function increases by about 30%. At the same time, further deterioration of testicular function may also result from an increase in the severity of nutcracker syndrome. The predictive model constructed in this study showed certain performance in both the training set and the verification set. Indicators such as C-index and AUC showed that the model had good discrimination ability.

This study still has some limitations. First, the relatively limited sample size was an important constraint. A total of 264 patients were included in this study. Although the training set and verification set were internally divided, for external verification, this sample size is difficult to fully represent the patient population in different regions and medical environments [18]. Second, patients from different regions have differences in genetic background, living environment, and dietary habits, which may have affected the pathogenesis, progression, and surgical reaction of varicocele and nutcracker syndrome [19]. Small sample size may not cover these differences, resulting in reduced reliability of external validation results. In addition, although the influencing factors included in this study were comprehensive, some potentially important factors might be missed. For example, genetic polymorphisms that may have affected an individual's response to surgery and the recovery of testicular function were tested in this study. Environmental factors such as long-term exposure to harmful substances and high-temperature environments may also affect testicular function, but are not evaluated in detail in the study [20]. These missing factors may play an important role in different regions and different populations, resulting in deviations in external verification. Finally, the contribution of the female to fertility outcome was not taken into account. In order to further improve the accuracy and reliability of the prediction model, a series of measures need to be taken in the future research to provide more robust data support and optimize the predictive model.

In summary, the predictive model and nomogram constructed in this study are valuable for evaluating the therapeutic effect of microscopic inferior epigastric-internal spermatic vein surgery. Although not verified by external data from other centers, these results still provide meaningful references for clinical practice. Future studies need to overcome the limitations, further improve the predictive model, and provide a more accurate basis for treatment decision-making.

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Disclosure of conflict of interest

None.

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